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(54) Title: GENES ESSENTIAL FOR MICROBIAL PROLIFERATION AND ANTISENSE THERETO

(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms as well as to screen for antimicrobial agents.

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GENES ESSENTIAL FOR MICROBIAL PROLIFERATION AND ANTISENSE THERETO

BACKGROUND OF THE INVENTION

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited. Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common Staphylococcus aureus (staph). This organism is commonly found in our environment and is responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by stubborn strains of bacteria, like staph. In short, the bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

There are a number of causes for the predicament in which practitioners of medical arts find themselves. Over-prescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patient is also partly responsible, for even in instances where an antibiotic is the appropriate treatment, patients will often improperly use the drug, the result being yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial scourges that have haunted humanity remain, in spite of the development of modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now advancing on the health of humanity. A new generation of antibiotics to once again deal with the pending health threat that bacteria present is required.

Discovery of New Antibiotics

As more and more bacterial strains become resistant to the panel of available antibiotics, new compounds are required. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug is nearly US \$500 million, and the

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average time is 15 years from laboratory to patient. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of an organism make for excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the organism. Once a target is identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Using physical and computational techniques, to analyze structural and biochemical targets in order to derive compounds that interact with a target is called rational drug design and offers great future potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

Escherichia coli represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6 x 10⁶ base pairs of the Escherichia coli (E. coli) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire E. coli genome has been sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the metB-malB Region of Escherichia coli K12, 1975, J. Bacteriol. 126: 48-55).

Novel, safe and effective antimicrobial compounds are needed in view of the rapid rise of antibiotic resistant microorganisms. However, prior to this invention, the characterization of even a single bacterial gene was a painstaking process, requiring years of effort. Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that

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encode gene products required for proliferation and for methods to identify molecules that interact with and alter the functions of such genes and gene products.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 1-127, wherein expression of said nucleic acid inhibits proliferation of a microorganism. The nucleic acid sequence may be complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a microorganism. The nucleic acid sequence may be complementary to at least a portion of an RNA required for proliferation of a microorganism. The RNA may be an RNA encoding more than one gene product.

Another embodiment of the present invention is a nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-127, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive bases of one of SEQ ID NOs: 1-127.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid sequences of each of the preceding paragraphs. The promoter may be active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a host cell containing the vectors of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 128-298.

Another embodiment of the present invention is a fragment of the nucleic acid of the preceding paragraph, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 128-298.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid of the preceding two paragraphs.

Another embodiment of the present invention is a purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding

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region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-127, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127, the sequences complementary to SEQ ID NOs.: 1-127 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127 as determined using BLASTN version 2.0 with the default parameters. The nucleic acid may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Staphylococcus aureus, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127. The polypeptide may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-469.

Another embodiment of the present invention is a host cell containing the vector of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides. The polypeptide may comprise a polypeptide comprising one of SEQ ID NOs.: 299-469 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least

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50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127 as determined using FASTA version 3.0t78 with the default parameters. The polypeptide may have at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-469 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-469 as determined using FASTA version 3.0t78 with the default parameters.

Another embodiment of the present invention is an antibody capable of specifically binding one of the polypeptides of the preceding paragraph.

Another embodiment of the present invention is a method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 into a cell. The method may further comprise the step of isolating said polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting said gene product with a candidate compound and determining whether said compound influences the activity of said gene product. The gene product may be a polypeptide and said activity may be an enzymatic activity. The gene product may be a polypeptide and said activity may be a carbon compound catabolism activity. The gene product may be a polypeptide and said activity may be a biosynthetic activity. The gene product may be a polypeptide and said activity may be a transporter activity. The gene product may be a polypeptide and said activity may be a transcriptional activity. The gene product may be a polypeptide and said activity may be a DNA replication activity. The gene product may be a polypeptide and said activity my be a cell division activity. The gene product may be a polypeptide and said activity my be a cell division activity. The gene product may be a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

AThe method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

- (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
 - (b) contacting said target with a candidate compound or nucleic acid; and
 - (c) measuring an activity of said target.

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The target may be a messenger RNA molecule and said activity may be translation of said messenger RNA. The target may be a messenger RNA molecule and said activity may be transcription of a gene encoding said messenger RNA. The target may be a gene and said activity may be transcription of said gene. The target may be a nontranslated RNA and said activity may be processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex. The target gene or RNA may encode a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound or nucleic acid identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising the steps of:

- (a) expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;
 - (b) contacting said sensitized cell with a compound; and
 - (c) determining whether said compound inhibits the growth of said sensitized cell.

The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The cell may be an E. coli cell. The cell may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae,

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Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level. Growth inhibition may be measured by monitoring optical density of a culture growth solution. The gene product may be a polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-469. The gene product may be an RNA.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a compound with activity against the product of said gene into a population of cells expressing said gene. The compound may be an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof. The proliferation inhibiting portion of one of SEQ ID NOs.: 1-127 may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive bases of one of SEQ ID NOs.: 1-127. The population may be a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The population may be a population of Gram negative bacteria. The population may be a population of E. coli cells. The population may be a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis cells or cells from any species falling within the genera of any of the above species. The gene may encode a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof in a pharmaceutically

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acceptable carrier. The proliferation-inhibiting portion of one of SEQ ID NOs.: 1-127 may comprise at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon. The antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a proliferation inhibiting portion thereof.

The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population. The cell may be contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid. The cell may be contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a ribozyme into said cellpopulation, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide. The cell may be contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell. The cell may be contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid. The antisense nucleic acid may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127. The antisense nucleic acid may be an oligonucleotide.

Another embodiment of the present invention is a method for identifying a gene which is required for proliferation of a microorganism comprising:

- (a) contacting a microorganism other than *E. coli* with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127;
- (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
- (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.

 The microorganism may be a Gram negative bacterium. The microorganism may be selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus

neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The method may further comprise introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.

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Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:

- (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127;
- (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
- (c) contacting said first microorganism with a sublethal level of said inhibitory nucleic acid, thus sensitizing said first microorganism;
 - (d) contacting the sensitized microorganism of step (c) with a compound; and
- (e) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism. Step (a) may comprise identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEO ID NOs. 1-127 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database. Step (a) may comprise identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene. Step (a) may comprise expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 in said microorganism. The inhibitory nucleic acid may be an antisense nucleic acid. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of said homolog. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of the operon encoding said homolog. The step of contacting the first microorganism with a sublethal

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level of said inhibitory nucleic acid may comprise directly contacting said microorganism with said inhibitory nucleic acid. The step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid may comprise expressing an antisense nucleic acid to said homolog in said microorganism. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method of identifying a compound having the ability to inhibit proliferation comprising:

- (a) contacting a microorganism other than *E. coli* with a sublethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
 - (b) contacting the sensitized microorganism of step (a) with a compound; and
- (c) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having activity against a biological pathway required for proliferation comprising:

- (a) sensitizing a cell by expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, in said cell to reduce the activity or amount of said gene product;
 - (b) contacting the sensitized cell with a compound; and
 - (c) determining whether said compound inhibits the growth of said sensitized cell.

The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The Gram negative bacterium may be E. coli. The cell may be selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae,

Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level. The inhibition of proliferation may be measured by monitoring the optical density of a liquid culture. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit cellular proliferation comprising:

- (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127;
 - (b) contacting said cell with a compound; and

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(c) determining whether said compound reduces proliferation of said contacted cell. The determining step may comprise determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise an antisense nucleic acid to a gene or operon required for proliferation. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise a compound known to inhibit growth or proliferation of a microorganism. The cell may contain a mutation which reduces the activity or level of said gene product required for proliferation of said cell. The mutation may be a temperature sensitive mutation. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

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(a) expressing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;

- (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
- (c) determining whether said cell is sensitive to said compound.

 The determining step may comprise determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid and wherein said gene or gene product lies in the same pathway on which said compound acts if said cell expressing said sublethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sublethal level of said antisense nucleic acid.

The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

Another embodiment of the present invention is a method for determining the biological pathway on which a test compound acts comprising:

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- (a) expressing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
 - (b) contacting said cell with said test compound; and
 - (c) determining whether said cell is sensitive to said test compound.

The determining step may comprise determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid. The method may further comprise:

- (d) expressing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and
- (e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127.

Another embodiment of the present invention is a compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.

Another embodiment of the present invention is a compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.

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Another embodiment of the present invention is a method for manufacturing an antibiotic comprising the steps of screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and manufacturing the compound so identified.

The screening step may comprise performing any one of the methods of identifying a compound described above.

Another embodiment of the present invention is a method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 to said subject. The method of subject may be selected from the group consisting of vertebrates, mammals, avians, and human beings. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli* ribosomal protein rplW (AS-rplW) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the elaD gene (AS-elaD) which is not known to be involved in protein synthesis and which is also essential for proliferation.

Figure 2A is a tetracycline dose response curve in $\it E.~coli$ transformed with an IPTG-inducible plasmid containing antisense to rplW gene (AS-rplW) carried out in the presence of 0, 20 or 50 μ M IPTG.

Figure 2B is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to elaD gene (AS-elaD) carried out in the presence of 0, 20 or $50 \mu M$ IPTG.

Figure 3 is a graph showing the fold increase in tetracycline sensitivity of *E. coli* transfected with antisense clones to essential ribosomal protein genes L23 (AS-rplW) and L7/L12

and L10 (AS-rplLrplJ). Antisense clones to genes known not to be involved in protein synthesis (atpB/E(AS-atpB/E), visC (AS-visC, elaD (AS-elaD), yohH (AS-yohH) are much less sensitive to tetracycline.

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Definitions

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as cell walls. Biological pathways that are usually required for proliferation of microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

By "inhibit activity of a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene or to reduce the level or activity of a product of the gene. Agents which inhibit the activity of a gene include agents that inhibit transcription of the gene, agents that inhibit processing of the transcript of the gene, agents that reduce the stability of the transcript of the gene, and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which inhibit the activity of a gene can act to decrease expression of the operon in which the gene resides or alter the folding or processing of operon RNA so as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as ribosomal RNA, a translated RNA (mRNA) or the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are antisense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell.

By "activity against a nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell.

By "activity against a gene" is meant having the ability to inhibit the function or expression of the gene in a cell.

By "activity against an operon" is meant having the ability to inhibit the function or reduce the level of one or more products of the operon in a cell.

By "antibiotic" is meant an agent which inhibits the proliferation of a microorganism.

By "identifying a compound" is meant to screen one or more compounds in a collection of compounds such as a combinatorial chemical library or other library of chemical compounds or to characterize a single compound by testing the compound in a given assay and determining whether it exhibits the desired activity.

By "inducer" is meant an agent or solution which, when placed in contact with a microorganism, increases transcription from a desired promoter.

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As used herein, "nucleic acid" means DNA or RNA. Thus, the terminology "the nucleic acid of SEQ ID NO: X" includes both the DNA sequence of SEQ ID NO: X and an RNA sequence in which the thymidines in the DNA sequence have been substituted with uridines in the RNA sequence and in which the deoxyribose backbone of the DNA sequence has been substituted with a ribose backbone in the RNA sequence.

As used herein, "sublethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a group of E. coli genes and gene families required for growth and/or proliferation. A proliferation-required gene or gene family is one where, in the absence of a gene transcript and/or gene product, growth or viability of the microorganism is reduced or eliminated. Thus, as used herein the terminology "proliferation-required" or "required for proliferation" encompasses sequences where the absence of a gene transcript and/or gene product completely eliminates cell growth as well as sequences where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses novel assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds. The present invention also describes methods for identification of homologous genes in organisms other than E. coli.

The present invention utilizes a novel method to identify proliferation-required *E. coli* sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted into an inducible expression vector, thus forming an expression library. Although the insert nucleic acids may be derived from the chromosome of the organism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term expression is defined as the production of an RNA molecule from a gene, gene fragment, genomic

fragment, or operon. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into an *E. coli* population to search for genes that are required for bacterial proliferation. Because the library molecules are foreign to the population of *E. coli*, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

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Expression of the exogenous nucleic acid fragments in the test population of *E. coli* containing the expression vector library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid sequences carried by the expression vector library. The test population of *E. coli* cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that, upon activation and expression, negatively impact the growth of the *E. coli* screen population were identified, isolated, and purified for further study.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in *E. coli* cultures expressing exogenous nucleic acid sequences and growth in cultures not expressing these sequences is compared. Growth measurements are assayed by examining the extent of growth by measuring optical densities. Alternatively, enzymatic assays can be used to measure bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that failed to grow or grow with reduced efficiency under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acid sequences of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleic acid sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a sequence of interest is sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleic acid sequence.

Determination of sequence source is achieved by comparing the obtained sequence data with known sequences in various genetic databases. The sequences identified are used to probe these gene databases. The result of this procedure is a list of exogenous nucleic acid sequences corresponding to a list that includeds novel bacterial genes required for proliferation as well as genes previously identified as required for proliferation.

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The number of DNA and protein sequences available in database systems has been growing exponentially for years. For example, at the end of 1998, the complete sequences of *Caenorhabditis elegans*, *Saccharomyces cerevisiae* and nineteen bacterial genomes, including *E. coli* were available. This sequence information is stored in a number of databanks, such as GenBank (the National Center for Biotechnology Information (NCBI), and is publicly available for searching.

A variety of computer programs are available to assist in the analysis of the sequences stored within these databases. FastA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63-98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl. Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleic acid sequences.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences. The genes of an operon are co-transcribed and are often related functionally. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid sequence corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation. Accordingly, determining which of the genes that are encoded within the operons are individually required for proliferation is often desirable.

In one embodiment of the present invention, an operon is dissected to determine which gene or genes are required for proliferation. For example, the RegulonDB DataBase described by Huerta et al. (Nucl. Acids Res. 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, may be used. to identify the boundaries of operons encoded within microbial genomes. A number of techniques that are well known in the art can be used to dissect the operon. In one aspect of this embodiment, gene disruption by homologous recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of homologous recombination. The method described by Link et al. (J. Bacteriol 1997 179:6228) serves as an excellent example of these methods as applicable to disruption of genes in *E. coli*. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that sequences adjacent to the wild type gene (ca. 500 bp) are retained. These homologous sequences surrounding the deletion null allele provide targets for homologous recombination so that the wild type gene on the *E. coli* chromosome can be replaced by the constructed null allele.

The crossover PCR amplification product is subcloned into the vector pKO3, the features of which include a chloramphenicol resistance gene, the counter-selectable marker sacB, and a temperature sensitive autonomous replication function. Following transformation of an E. coli cell population with such a vector, selection for cells that have undergone homologous recombination of the vector into the chromosome is achieved by growth on chloramphenicol at the non-permissive temperature of 43°C. Under these conditions, autonomous replication of the plasmid cannot occur and cell are resistant to chloramphinicol only if the chloramphenicol resistance gene has been integrated into the chromosome. Usually a single crossover event is responsible for this integration event such that the E. coli chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence.

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This new *E. coli* strain containing the tandem duplication can be maintained at permissive temperatures in the presence of drug selection (chloramphenicol). Subsequently, cells of this new strain are cultured at the permissive temperature 30°C without drug selection. Under these conditions, the chromosome of some of the cells within the population will have undergone an internal homologous recombination event resulting in removal of the plasmid sequences. Subsequent culturing of the strain in growth medium lacking chloramphenicol but containing sucrose is used to select for such recombinative resolutions. In the presence of the counter-selectable marker *sacB*, sucrose is rendered into a toxic metabolite. Thus, cells that survive this counter-selection have lost both the plasmid sequences from the chromosome and the autonomously replicating plasmid that results as a byproduct of recombinative resolution.

There are two possible outcomes of the above recombinative resolution via homologous recombination. Either the wild type copy of the targeted gene is retained on the chromosome or the mutated null allele is retained on the chromosome. In the case of an essential gene, a single copy of the null allele would be lethal and such cells should not be obtained by the above procedure when applied to essential genes. In the case of a non-essential gene, roughly equal numbers of cells containing null alleles and cells containing wild type alleles should be obtained. Thus, the method serves as a test for essentiality of the targeted gene: when applied to essential genes, only cells with a wild type allele on the chromosome will be obtained.

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Other techniques have also been described for the creation of disruption mutations in *E. coli*. For example, Link et al. also describe inserting an in-frame sequence tag concommitantly with an in-frame deletion in order to simplify analysis of recombinants obtained. Further, Link et al. describe disruption of genes with a drug resistance marker such as a kanamycin resistance gene. Arigoni et al., (Arigoni, F. et al. A Genome-based Approach for the Identification of Essential Bacterial Genes, Nature Biotechnology 16: 851-856) describe the use of gene disruption combined with engineering a second copy of a test gene such that the expression of the gene is regulated by and inducible promoter such as the arabinose promoter to test the essentiality of the gene. Many of these techniques result in the insertion of large fragments of DNA into the gene of interest, such as a drug selection marker. An advantage of the technique described by Link et al. is that it does not rely on an insertion into the gene to cause a functional defect, but rather results in the precise removal of the coding region. This insures the lack of polar effects on the expression of genes downstream from the target gene.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene identified as required for proliferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the sequences encoding a signal peptide to facilitate secretion of the expressed protein.

Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 75, or more than 75 consecutive amino acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain sequences upstream and downstream of the coding sequence.

When expressing the coding sequence of an entire gene identified as required for bacterial proliferation or a fragment thereof, the nucleic acid sequence to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767. Fusion protein expression systems are also contemplated by the present invention.

Following expression of the protein encoded by the identified exogenous nucleic acid sequence, the protein is purified. Protein purification techniques are well known in the art. Proteins

encoded and expressed from identified exogenous nucleic acid sequences can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Chromatographic methods usable with the present invention can include ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography. Electrophoretic methods such one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising antibody columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene coding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the identified exogenous nucleic acid sequences. Both monoclonal and polyclonal antibodies can be generated against the expressed proteins. Methods for generating monoclonal and polyclonal antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

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Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene sequence is contemplated by the present invention.

The present invention further contemplates utility against a variety of other pathogenic organisms in addition to E. coli. For example, the invention has utility in identifying genes required for proliferation in prokaryotes and eukaryotes. For example, the invention has utility with protists, such as Plasmodium spp.; plants; animals, such as Entamoeba spp. and Contracaecum spp; and fungi including Candida spp., (e.g., Candida albicans), Saccharomyces cerevisiae, Cryptococcus neoformans, and Aspergillus fumigatus. In one embodiment of the present invention, monera, specifically bacteria are probed in search of novel gene sequences required for proliferation. This embodiment is particularly important given the rise of drug resistant bacteria.

The numbers of bacterial species that are becoming resistant to existing antibiotics are growing. A partial list of these organisms includes: Staphylococcus spp., such as S. aureus; Enterococcus spp., such as E. faecalis; Pseudomonas spp., such as P. aeruginosa, Clostridium spp., such as C. botulinum, Haemophilus spp., such as H. influenzae, Enterobacter spp., such as E. cloacae, Vibrio spp., such as V. cholera; Moraxala spp., such as M. catarrhalis; Streptococcus spp., such as S. pneumoniae, Neisseria spp., such as N. gonorrhoeae; Mycoplasma spp., such as

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Mycoplasma pneumoniae; Salmonella typhimurium; Helicobacter pylori; Escherichia coli; and Mycobacterium tuberculosis. The sequences identified as required for proliferation in the present invention can be used to probe these and other organisms to identify homologous required proliferation genes contained therein.

In one embodiment of the present invention, the nucleic acid sequences disclosed herein are used to screen genomic libraries generated from bacterial species of interest other than E. coli. For example, the genomic library may be from Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. Standard molecular biology techniques are used to generate genomic libraries from various microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences. The homologous sequences identified can then be used as targets for the identification of new, antimicrobial compounds with activity against more than one organism.

For example, the preceding methods may be used to isolate nucleic acids having a sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% identity to a nucleic acid sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-127, 128-298, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive bases thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)). For example, the homologous polynucleotides may have a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of SEQ ID NOs: 1-127, 128-298 or the sequences complementary thereto.

Additionally, the above procedures may be used to isolate nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, or at least 40% identity or similarity to a polypeptide having the sequence of one of SEQ ID NOs: 299-469or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78

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algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Alschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)).

Alternatively, homologous nucleic acids or polypeptides may be identified by searching a database to identify sequences having a desired level of homology to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids or polypeptides having at least 97%, at least 95%, at least 95%, at least 85%, at least 80%, at least 70%, at least 60%, or at least 50%, at least 40% identity or similarity to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid involved in proliferation. For example, the database may be screened to identify nucleic acids homologous to one of SEQ ID Nos. 1-127, 128-298 or polypeptides homologous to SEQ ID NOs. 299-469. In some embodiments, the database may be screened to identify homologous nucleic acids or polypeptides from organisms other than E. coli, including organisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species.

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrane, or the like. Such arrays can be used by researchers to quantify relative gene expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5807522.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays from Genosys consist of 12 x 24 cm nylon filters containing PCR products corresponding to 4290 ORFs from *E. coli*. 10 ngs of each are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done by phosphorimager.

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Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid against a proliferation-required gene. Analysis of the expression pattern indicated by hybridization to the array provides information on whether or not the target gene of the antisense nucleic acid is being affected by antisense induction, how quickly the antisense is affecting the target gene, and for later timepoints, what other genes are affected by antisense expression. For example, if the antisense is directed against a gene for ribosomal protein L7/L12 in the 50S subunit, its targeted mRNA may disappear first and then other mRNAs may be observed to increase, decrease or stay the same. Similarly, if the antisense is directed against a different 50S subunit ribosomal protein mRNA (e.g. L25), that mRNA may disappear first followed by changes in mRNA expression that are similar to those seen with the L7/L12 antisense expression. Thus, the mRNA expression pattern observed with an antinsense nucleic acid against a proliferation required gene may identify other proliferation-required nucleic acids in the same pathway as the target of the antisense nucleic acid. In addition, the mRNA expression patterns observed with candidate drug compounds may be compared to those observed with antisense nucleic acids against a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of candidate drug compounds for use in screening methods such as those described below.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different organisms, gene expression arrays can identify homologous genes in the two organisms.

The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In this embodiment, the conserved portions of sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene is expressed in an autologous organism or

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in a heterologous organism in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologus organism. In still another aspect of this embodiment, the homologous gene or portion is expressed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous organism.

The homologous sequences to proliferation-required genes identified using the techniques described herein may be used to identify proliferation-required genes of organisms other than *E. coli*, to inhibit the proliferation of organisms other than *E. coli* by inhibiting the activity or reducing the amount of the identified homologous nucleic acid or polypeptide in the organism other than *E. coli*, or to identify compounds which inhibit the growth of organisms other than *E. coli* as described below.

In another embodiment of the present invention, *E. coli* sequences identified as required for proliferation are transferred to expression vectors capable of function within non-*E coli* species. As would be appreciated by one of ordinary skill in the art, expression vectors must contain certain elements that are species specific. These elements can include promoter sequences, operator sequences, repressor genes, origins of replication, ribosomal binding sequences, termination sequences, and others. To use the identified exogenous sequences of the present invention, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into an expression vector adapted for use in the species of bacteria to be screened.

Expression vectors for a variety of other species are known in the art. For example, Cao et al. report the expression of steroid receptor fragments in *Staphylococcus aureus*. J. Steroid Biochem Mol Biol. 44(1):1-11 (1993). Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: *Salmonella typhimurium*, *Pseudomonas putida*, and *Pseudomonas aeruginosa*. J. Bacteriol. 172(8):4448-55 (1990). These examples demonstrate the existence of molecular biology techniques capable of constructing expression vectors for the species of bacteria of interest to the present invention.

Following the subcloning of the identified nucleic acid sequences into an expression vector functional in the microorganism of interest, the identified nucleic acid sequences are conditionally transcribed to assay for bacterial growth inhibition. Those expression vectors found to contain sequences that, when transcribed, inhibit bacterial growth are compared to the known genomic sequence of the pathogenic microorganism being screened or, if the homologous sequence from the organism being screened is not known, it may be identified and isolated by hybridization to the proliferation-required *E. coli* sequence interest or by amplification using primers based on the proliferation-required *E. coli* sequence of interest as described above.

The antisense sequences from the second organism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, and introduced into the

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second organism. The techniques described herein for identifying *E. coli* genes required for proliferation may thus be employed to determine whether the identified sequences from a second organism inhibit the proliferation of the second organism.

Antisense nucleic acids required for the proliferation of organisms other than E. coli or the genes corresponding thereto, may also be hybridized to a microarray containing the E. coli ORFs to gauge the homology between the E. coli sequences and the proliferation-required nucleic acids from other organisms. For example, the proliferation-required nucleic acid may be from Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni or Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. The proliferation-required nucleic acids from an organism other than E. coli may be hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the sequence on the microarray. This would provide an indication of homology across the organisms as well as clues to other possible essential genes in these organisms.

In still another embodiment, the exogenous nucleic acid sequences of the present invention that are identified as required for bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be directed against the proliferation-required genes whose sequence corresponds to the exogenous nucleic acid probes identified here (i.e. the antisense nucleic acid may hybridize to the gene or a portion thereof). Alternatively, antisense therapeutics can be directed against operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to any gene in the operon in which the proliferation-required genes reside). Further, antisense therapeutics can be directed against a proliferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acid sequences complementary to sequences required for proliferation as diagnostic tools. For example, nucleic acid probes complementary to proliferation-required sequences that are specific for particular species of microorganisms can be used as probes to identify particular microorganism species in clinical specimens. This utility provides a rapid and dependable method by which to identify

the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to prescribe species specific antimicrobial compounds to treat such infections. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences can also be used to screen for specific microorganisms that produce such proteins in a species-specific manner.

The following examples teach the genes of the present invention and a subset of uses for the *E. coli* genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

EXAMPLES

The following examples are directed to the identification and exploitation of *E. coli* genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences.

Genes Identified as Required for Proliferation of E. coli

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Exogenous nucleic acid sequences were cloned into an inducible expression vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of exogenous nucleic acid sequences cloned into the IPTG-inducible expression vector pLex5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)). Upon activation or induction, the expression vectors produced an RNA molecule corresponding to the subcloned exogenous nucleic acid sequences. The RNA product was in an antisense orientation with respect to the *E. coli* genes from which it was originally derived. This antisense RNA then interacted with sense mRNA produced from various *E. coli* genes and interfered with or inhibited the translation of the sense messenger RNA (mRNA) thus preventing protein production from these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for the proliferation, bacterial cells containing an activated expression vector failed to grow or grew at a substantially reduced rate. Similar results have also be obtained in cases where the gene encodes a non-translated RNA, such as a ribosomal RNA.

EXAMPLE 1

Inhibition of Bacterial Proliferation after IPTG induction

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2 , 10^3 , 10^4 , 10^5 , 10^6 , 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 μ l of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as containing a sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid

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sequence corresponds, or a gene within the operon containing the inserted nucleic acid, may be required for proliferation in *E. coli*.

Characterization of Isolated Clones Negatively Affecting E. coli Proliferation

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Following the identification of those expression vectors that, upon expression, negatively impacted *E. coli* growth or proliferation, the inserts or nucleic acid fragments contained in those expression vectors were isolated for subsequent characterization. Inserts in expression vectors of interest were subjected to nucleic acid sequence determination.

EXAMPLE 2

Nucleic Acid Sequence Determination of Identified Clones Expressing Nucleic Acid Fragments with Detrimental Effects of E. coli Proliferation

The nucleotide sequences for the exogenous identified sequences were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia, CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 1) and 5' - ACAATTTCACACAGCCTC - 3' (SEQ ID NO: 2). These sequences flank the polylinker in pLEX5BA. Sequence identification numbers (SEQ ID NOs) for the identified inserts are listed in Table I and discussed below.

EXAMPLE 3

Comparison Of Isolated Sequences to Known Sequences

The nucleic acid sequences of the subcloned fragments obtained from the expression vectors discussed above were compared to known *E. coli* sequences in GenBank using BLAST version 1.4 or version 2.0.6 using the following default parameters: Filtering off, cost to open a gap=5, cost to extend a gap=2, penalty for a mismatch in the blast portion of run=-3, reward for a match in the blast portion of run=1, expectation value (e)=10.0, word size=11, number of one-line descriptions=100, number of alignments to show (B)=100. BLAST is described in Altschul, J Mol Biol. 215:403-10 (1990). Expression vectors were found to contain nucleic acid sequences in both the sense and antisense orientations. The presence of known genes, open reading frames, and ribosome binding sites was determined by comparison to public databases holding genetic information and various computer programs such as the Genetics Computer Group programs FRAMES and CODONPREFERENCE. Clones were designated as "antisense" if the cloned fragment was oriented to the promoter such that the RNA transcript produced was complementary to the expressed mRNA from a chromosomal locus. Clones were designated as "sense" if they coded for an RNA fragment that was identical to a portion of a wild type mRNA from a chromosomal locus.

The sequences described in Examples 1-2 that inhibited bacterial proliferation and contained gene fragments in an antisense orientation are listed in Table I. This table lists each identified sequence by: a sequence identification number, a Molecule Number, a gene to which the identified sequence corresponds, listed according to the National Center for Biotechnology Information (NCBI), Blattner

(Science 277:1453-1474(1997); also contains the *E. coli* K-12 genome sequence), or Rudd (Micro. and Mol. Rev. 62:985-1019 (1998)), nomenclatures. The CONTIG numbers for each identified sequence is shown, as well as the location of the first and last base pairs located on the *E. coli* chromosome. A Molecule Number with a "**" indicates a clone corresponding to an intergenic sequence.

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TABLE I

Identified Clones with Corresponding Genes and Operons

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
•	, ID .	No.	· (NCBI)	(Blat-	(Rudd)			÷ .•
				tner)				
626.O24	1	EcXA056	f320	b1113	ycfS	AE000211	7631	7971
E1M10000116B1	2	EcXA056b	ycfS	b1113	ycfS	AE000211	7658	7847
E1M10000155F12	3	EcXA056c	ycfS	b1113	ycfS	AE000211	7649	8037
Z56-D2	4	EcXA057	arp	b4017	arp	AE000474	14059	14440
E1M10000144B6	5	EcXA057b	arp	b4017	агр	AE000474	14187	14385
Z60-P16	6	EcXA058	rplC	ь3320	rplC	AE000408	10002	10338
Z80-D10	7	EcXA059	урјА	b2647	урјА	AE000349	10402	10493
						AE000350	1	728
P33-1.C22	8	EcXA060	rplR	b3304	rplR	AE000408	2763	2958
E1M10000161C06	9	EcXA060b	RplR;	b3304;	RplR;	AE000408	3006	3477
			rplF	b3305	rplF			
P35-7	10	EcXA061	malE	ь4034	malE	AE000476	11925	12089
P35-8	11	EcXA062	rep	ь3778	rep	AE000454	4438	4111
P38-1.G20	12	EcXA063	elaD	b2269	elaD	AE000316	9912	9581
E1M10000107H4	13	EcXA063b	elaD	b2269	claD	AE000316	9520	9389
E1M10000122B03	14	EcXA063c	elaD	b2269	elaD	AE000316	9979	9715
E1M10000139B07	15	EcXA063d	elaD	b2269	claD	AE000316	10171	9533
E1M10000152G3	16	EcXA063e	elaD	b2269	elaD	AE000316	9535	9406
E1M10000143G03	17	EcXA063f	elaD	ь2269	claD	AE000316	10104	9869
E1M10000131H01	18	EcXA063h	elaD	b2269	elaD	AE000316	9953	9746
P319-4.06	19	EcXA064	CyoE	b0428	cyoE	AE000149	2140	2293
P323-1.M10	20	EcXA065	DgoA	b3692	YidU	AE000446	6005	6272
E1M10000111E4	21	EcXA065b	DgoA	b3692	YidU	AE000446	6005	6133
P323-8.P1	22	EcXA066	Rpml	b1717	RpmI	AE000266	10240	10390

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000137G09	23	EcXA066b	RplT;r	b1716;	RplT;	AE000266	9947	10525
			pmI	b1717	RpmI			
P326-22.E17	24	EcXA067	xylF	b3566	XylF	AE000434	288	95
P326-9.K2	25	EcXA068	YhfL;	b3369;	yhfL;	AE000413	581	306
			yhfM	ь3370	yhfM			
P327-50.M10	26	EcXA069	RplD;	b3319;	rplD;	AE000408	9747	9900
			rplC	b3320	rplC			
E1M10000110G1	27	EcXA069b	RplD;	b3319;	rplD;	AE000408	9789	9933
			rplC	ь3320	rplC			
E1M10000121D08	28	EcXA069c	RplD;	b3319;	RplD;	AE000408	9737	10002
			rplC	ь3320	rplC			
E1M10000136H1	29	EcXA069d	RplD;	b3319;	RplD;	AE000408	9707	10241
			rplC	ь3320	rplC			
E1M10000126E08	30	EcXA069e	rplC	b3320	RpIC	AE000408	10157	10379
E1M10000137C04	31	EcXA069f	RplD;	b3319;	RplD;	AE000408	9783	10007
			rplC	b3320	RplC '			
E1M10000106G02	32	EcXA069g	rplC	b3320	RplC	AE000408	9814	10154
E1M10000146H01	33	EcXA069h	RplD;	ь3319;	RplD;	AE000408	9715	9890
			rplC	b3320	RplC			
E1M10000148C02	34	EcXA069i	RplD;	ьзз19;	RpID;	AE000408	9740	9980
			rplC	b3320	RplC			
P328-20.P20	35	EcXA070	YbcQ	b0551	YbcQ	AE000160	7883	7661
1065-12	36	EcXA071	ffh	b2610	Ffh	AE000346	11978	12129
						AE000347	1	319
E1M10000101D6	37	EcXA071b	RpsP;	b2609;	RpsP;	AE000346	11911	12129
			ffh	ь2610	ffh			
						AE000347	1	348
P332-11.C20	38	EcXA072	recJ	ь2892	recJ	AE000372	12047	12144
						AE000273	1	108
P334-5.H2	39	EcXA073	htrE	ь0139	htrE	AE000123	5431	5548
P338-4.M21	40	EcXA073b	htrE	b0139	htrE	AE000123	5447	5593
E1M10000119A04	41	EcXA073c	htrE	ь0139	htrE	AE000123	5419	5642
E1M10000137C03	42	EcXA073d	htrE;	b0139;	htrE;	AE000123	5414	5919
			ecpD	ь0140	ecpD			
E1M10000124G03	43	EcXA073c	htrE	ь0139	htrE	AE000123	5332	5515
P334-8.L7	44	EcXA074	yciR	Ь1285	yciR	AE000226	8045	8371
1053-37	45	EcXA074b	yciR	ь1285	yciR	AE000226	6079	6293
P335-3.J14	46	EcXA075	SfmD	b0532	sfmD	AE000159	3235	3115
P335-8.H8	47	EcXA076	mviM	ь1068	mviM	AE000207	11140	10983
						AE000208	50	1
P342-3	48	EcXA077	B2145	b2145	yeiS	AE000303	9025	8831
i					•			

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Blat- (Rudd)			
				tner)				
E1M10000106G10	49	EcXA077b	B2145	b2145	yeiS	AE000303	9007	8841
E1M10000144F3	50	EcXA077c	B2145	b2145	yeiS	AE000303	9052	8827
X3S177-4	51	EcXA078	ycgB	Ы 188	ycgB	AE000217	3945	4129
P317-2.A3	52	EcXA079	yedV	Ы968	yedX	AE000288	5289	5475
E1M10000151C04	53	EcXA079b	yedV	b1968	yedV	AE000288	5179	5515
E1M10000162G05	54	EcXA079c	yedV	b1968	yedV	AE000288	5313	5503
E1M10000167F04	55	EcXA079d	yedV	ь1968	yedV	AE000288	5293	5531
E1M10000167G04	56	EcXA079e	yedV	b1968	yed V	AE000288	5293	5531
X3S204-7	57	EcXA080	rplV	b3315	RplV	AE000408	7444	7770
E1M10000111C3	58	EcXA080b	RpIV;	b3315;	RplV;	AE000408	7633	7898
			rpsS	b3316	rpsS			
E1M10000131B07	59	EcXA080c	RpIV;	b3315;	RplV;	AE000408	7686	7871
•			rpsS	ь3316	rpsS			
E1M10000131C07	60	EcXA080d	RpIV;	b3315;	RpIV;	AE000408	7723	7860
·		. •	rpsS	b3316	rpsS ·	•		
E1M10000144G6	61	EcXA080e	rplV	b3315	RpIV	AE000408	7580	7762
E1M10000144C2	62	EcXA080f	RplV;	b3315;	RpIV;	AE000408	7650	7784
			rpsS	ь3316	rpsS			
E1M10000107G2	63	EcXA081	rpsP	b2609	RpsP	AE000346	11957	12097
MC9.6	64	EcXA082	hybC;	b2994;	HybC;	AE000382	4419	4562
			hybB	b2995	hybB			
B18-2.N21	65	EcXA083	hrpB	ь0148	HrpB	AE000124	3024	2955
P336-14.F20	66	EcXA084	B1399	ь1399	PaaX	AE000237	164	1
						AE000236	12073	12006
985.P21	67	EcXA085	AgaZ;	b3132;	agaZ;	AE000394	10111	10705
			agaV	ь3133	agaV			
Z92-K24	68	EcXA086	гplQ	b3294	RplQ	AE000407	7653	8349
E1M10000101C12	69	EcXA086b	грlQ	b3294	RplQ	AE000407	7748	8075
E1M10000103D11	70	EcXA086c	RplQ	b3294	RplQ	AE000407	7652	8051
E1M10000127D09	71	EcXA086d	rplQ;	ь3294;	RpIQ;	AE000407	7806	8129
			тро∧	b3295	rpoA			
E1M10000152D8	72	EcXA086e	rplQ;	b3294;	rplQ;	- AE000407	7950	8146
·			rpoA	b3295	rpoA			
SC17.1	73	EcXA087	YehW	b2128	YehW	AE000302	915	1226
SC21.1	74	EcXA088	RplO	ь3301	RplO	AE000408	1743	1907
E1M10000107G8	75	EcXA089	YadT	ь0158	YadT	AE000125	4489	4639
E1M10000115C6	76	EcXA090	DnaE	ь0184	DnaE	AE000127	10980	10830
EIM10000107B2	. 77	EcXA091	YkgE	b0306	YkgE	AE000137	9375	9261
E1M10000107C3	78	EcXA092	ь1497	ь1497	YdeM	AE000247	689	908
E1M10000107H9	79	EcXA093	YohM	b2106	YohM	AE000299	9423	9166
E1M10000109A11	80	EcXA094	YfjW	b2642	YfjW	AE000349	7160	6851

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000160D07	81	EcXA094b	YfjW	b2642	YfjW	AE000349	7118	6932
E1M10000161A05	82	EcXA094c	YfjW	b2642	YfjW	AE000349	6381	5980
E1M10000155A06	83	EcXA094d	YfjW	b2642	YfjW	AE000349	6893	6749
E1M10000111A7	84	EcXA095	ь2758	b2758	YgcJ	AE000359	4983	5069
E1M10000107E2	85	EcXA096	YgcM;	b2765;	ygcM;	AE000360	5320	5190
			ygcN	b2766	ygcN			
E1M10000115E3	86	EcXA097	yhcB	b3233	YhcB	AE000402	8070	7864
EIM10000107B3	87	EcXA097b	yhcB;	b3233;	yhcB;	AE000402	8168	7922
			degQ	b3234	degQ			;
E1M10000162F03	88	EcXA097c	yhcB	b3233	yhcB	AE000402	8111	7874
E1M10000127H07	89	EcXA097d?	yhcB	ь3233	yhcB	AE000402	8092	7808
E1M10000163C04	90	EcXA097e	yhcB;	b3233;	yhcB;	AE000402	8159	7874
			degQ?	b3234	degQ			
E1M10000115G2	91	EcXA098	rpoA	ь3295	RpoA	AE000407	8254	8453
E1M10000144A8	92	EcXA098b	RplQ;	b3294;	RpIQ;	AE000407	7841	8118
			гроА	ь3295	rpoA			
E1M10000101H9	93	EcXA099	RpsN;	ь3307;	RpsN;	AE000408	4403	4826
			фlE	ь3308	RplE			
E1M10000111F9	94	EcXA100	RpmH;	b3703;	RpmH;	AE000447	7555	7395
			mpA	b3704	RnpA			
E1M10000119D02	95	EcXA100b	rpmH;	ь3703;	RpmH;	AE000447	7581	7395
			mpA	ь3704	RnpA			
E1M10000106F05	96	EcXA100c	rpmH;	ь3703;	RpmH;	AE000447	7594	7359
			mpA	ь3704	RnpA			
E1M10000152H8	97	EcXA100d	RpmH;	ь3703;	RpmH;	AE000447	7630	7340
		•	mpA	ь3704	RnpA			
E1M10000115H1	98	EcXA101	yihK	b3871	TypA	AE000462	8811	8629
E1M10000101H7	99	EcXA102	adiY	b4116	AdiY	AE000484	1980	2171
E1M10000109A02	100	EcXA103	yjhB	b4279	YjhB	AE000498	8776	8536
E1M10000113A11	101	EcXA104	hsdS	b4348	HsdS	AE000505	6319	6495
E1M10000125A2	102	EcXA104b	hsdS	b4348	HsdS	AE000505	6277	6526
E1M10000103A5	103	EcXA105	ydaU	b1359	YdaU	AE000233	4497	4306
E1M10000135B2	104	EcXA106	ybbV	ь0510	YbbV	AE000157	3796	3624
EIM10000131G10	105	EcXA106	ybbV	ь0510	YbbV	AE000157	3796	3624
E1M10000110A12	106	EcXA107	yegO	ь2076	YegO	AE000297	14471	14330
E1M10000110E9	107	EcXA108	yigK	ь3824	YigK	AE000458	3709	3964
E1M10000133A06	108	EcXA109	modC	ь0765	ModC	AE000179	2414	2180
E1M10000133B08	109	EcXA110	ynaF;	b1376;	YnaF;	AE000234	8011	8149
			ь1377	ь1377	OmpN			
E1M10000106E09	110	EcXA110b	ynaF;	b1376;	YnaF;	AE000234	7967	8207
			ь1377	ь1377	OmpN			

Clone Name	Seq	Molecule	Gene	Gene	Gene	Contig	Start	Stop
	ID	No.	(NCBI)	(Blat-	(Rudd)			
				tner)				
E1M10000160G07	111	EcXA110c	ynaF;	b1376;	YnaF;	AE000234	7990	8114
			ь1377	b1377	OmpN			
SC13.1	112	EcXA110d	ynaF	ь1376	YnaF	AE000234	8027	8243
E1M10000155B05	113	EcXA110e	ynaF;	b1376;	YnaF;	AE000234	7992	8139
			ь1377	ь1377	ompN			
E1M10000133D09	114	EcXA111	ppdA	b2826	PpdA	AE000366	4876	5068
E1M10000162B08	115	EcXA111b	ppdA	b2826	PpdA	AE000366	4968	5084
E1M10000133E01	116	EcXA112	yrfF	b3398	YrfF	AE000415	5835	5712
E1M10000101A7	117	EcXA113	ybbQ;	ь0509;	YbbQ;	AE000157	3753	3466
			ybbV	ь0510	ybbV			
E1M10000131F04	118	EcXA113b	ybbQ;	ь0509;	YbbQ;	AE000157	3781	3536
. •			ybbV	b0510	ybbV			
E1M10000159A09	119	EcXA113c	ybbQ;	ь0509;	YbbQ;	AE000157	3781	3257
		,	ybbV	b0510	ybbV			
E1M10000166F09	120	EcXA113d	ybbV	ь0510	YbbV	AE000157	3784	3624
E1M10000121E07	121	EcXA114	b2352;	b2352;	YfdH;	AE000323	10110	9882
			b2353	b2353	yfdl			
						AE000324	357	1
E1M10000121F06	122	EcXA115	ygeF	b2850	YgeF	AE000369	570	304
E1M10000140B05	123	EcXA115b	ygcF	ь2850	YgeF	AE000369	512	312
E1M10000148H09	124	EcXA115c	ygeF	b2850	YgeF	AE000369	607	361
E1M10000164A02	125	EcXA115d	ygcF	b2850	YgcF	AE000369	555	411
E1M10000121G05	126	EcXA116	insB_3	b0021		AE000135	5258	5726
E1M10000136D3	127	EcXA117	rhsA	b3593	RhsA	AE000437	4125	3529

EXAMPLE 4

Identification of Genes and their Corresponding Operons Affected by Antisense Inhibition

The sequencing of the entire E. coli genome is described in Blattner et al., Science 277:1453-5 . 1474(1997) and the sequence of the genome is listed in GenBank Accession No.U00096. The operons to which the proliferation-inhibiting nucleic acids correspond were identified using RegulonDB and information in the literature. The coordinates of the boundaries of these operons on the E. coli genome are listed in Table III. Table II lists the molecule numbers of the inserts containing the growth inhibiting nucleic acid fragments, the genes in the operons corresponding to the inserts, the SEQ ID NOs of the genes containing the inserts, the SEQ ID NOs of the proteins encoded by the genes, the start and stop points of the genes on the E. coli genome, the orientation of the genes on the genome, whether the operons are predicted or documented, and the predicted functions of the genes. The identified operons, their putative functions, and whether or not the genes are presently thought to be required for proliferation are discussed below.

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Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. The functions for the genes of interest appear in Table II.

5 The proteins that are listed in Table II are involved in a wide range of biological functions.

TABLE II

All Operon Data with Whole Chromosome Coordinates

Molecule Number	Gene	Seq ID No.	Seq ID No.	Start	Stop	Operon	Blattner Functional Class	Predicted Function
		(gene)	(protein)					
EcXA056	ycfS	128	299	1168635	1169597	predicted operon	hypothetical, unclassified, unknown	
EcXA057	arp	129	300	4217880	4220066	predicted operon	Fatty acid and phospholipid metabolism	ankyrin repeat protein
EcXA058	rpsQ	130	301	3445951	3446205	documented	Translation, post- translational modification	
	rpmC	131	302	3446205	3446396		Translation, post- translational modification	
	rplP	132	303	3446396	3446806		Translation, post- translational modification	
	rpsC	133	304	3446819	3447520		Translation, post- translational modification	
	rplV	134	305	3447538	3447870		Translation, post- translational modification	
	rpsS	135	306	3447885	3448163		Translation, post- translational modification	- 0
	rplB	136	307	3448180	3449001		Translation, post- translational modification	translation
	rplW	137	308	3449019	3449321		Translation, post- translational modification	translation
	rplD	138	309	3449318	3449923		Translation, post- translational modification	Ļ
	rplC	139	310	3449934	3450563		Translation, post- translational modification	
	rpsJ	140	311	3450596	3450907		Translation, post- translational modification	
EcXA059	урјА	141	·312	2776167	2780876	predicted operon	Translation, post- translational modification	
EcXA060	rpmJ	142	313	3440255	3440371	documented	Translation, post- translational modification	
	prlA	143	314	3440403	3441734		Putative transport proteins	
	rp!O	144	315		3442176		Translation, post- translational modification	
	rpmD	145	316	3442180	3442359		Translation, post- translational modification	
	rpsE	146	317	3442363	3442866		Translation, post- translational modification	

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Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number	00	No.	No.			оре. о	Class	
		(gene)	(protein)					
	rplR	147	318	3442881	3443234	• • •	Translation, post-	
	rpik	147	210	J472001	3443234		translational modification	
	rplF	148	319	3443244	3443777		Translation, post-	translation
							translational modification	
	rpsH	149	320	3443790	3444182		Translation, post-	
							translational modification	
	rpsN	150	321	3444216	3444521		Translation, post-	
	•						translational modification	
	_15	151	322	3444536	3445075		Translation, post-	translation
	rplE	131	322	J444JJU	3443013		translational modification	uansanon
	rpIX	152	323	34450 9 0	3445404		Translation, post-	
							translational modification	
	rplN	153	324	3445415	3445786		Translation, post-	
							translational modification	
EcXA061	malE	154	325	4242808	4243998	documented	Transport and binding	
		, , , , ,					proteins	
	malF	155	326	4241110	4242654	•	Transport and binding	
				•	•		proteins	
	malG	156	327	4240205	4241095		Transport and binding	
				•			proteins	
EcXA062	гер	157	328	3958292	3960313	predicted	DNA replication,	
						operon	recombination,	
							modification and repair	
EcXA063	b2269	158	329	2380733	2381944	predicted	Putative enzymes	putative
						operon		phosphatase/sulfatase
EcXA064	cyoE	159	330	446039	446929	documented	Energy metabolism	
	cyoA	160	331	449887	450834		Energy metabolism	
	суоВ	161	332	447874	449865		Energy metabolism	
	суоС	162	333	447270	447884		Energy metabolism	
	cyoD	163	334	446941	447270		Energy metabolism	
EcXA065	dgoA	164	335	3869477	3871240	predicted	Carbon compound	2-Oxo-3-
							catabolism	deoxygalactonate 6-
								phosphate aldolase
	A V	165	1226	7071224	2072401		C	
	dgoK	165	336	3871224	3872401		Carbon compound catabolism	
	yidW	166	337	2972401	3872787			•
	y iu w	100	337	3872401	3012101		Hypothetical, unclassified, unknown	
	b3694	167	338	3872099	3872395		Putative regulatory	
	03034	.07	<i>33</i> G	36/2077	30/23/3		protein	
EcXA066	rplT	168	339	1797417	1797773	documented	Translation, post-	
20/21000			337			000000000000000000000000000000000000000	translational modification	
		1.00	240	1 = 0 = 0 0 (1500000			
	rpmI	169	340	1/9/826	1798023		Translation, post-	
							translational modification	
	infC	170	341	1798120	1798662		Translation, post-	translation
							translational modification	
	thrS	171	342	1798666	1800594		Translation, post-	
							translational modification	
EcXA067	xylF	172	343	3728760	3729752	:	Transport and binding	
DUM/IVU/	AJII.	112	J43	2120100	3127132	•	proteins	
EcXA068	yhfL	173	344	3497085	3497252	predicted	Hypothetical,	
	,			,	J	орегол	unclassified, unknown	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number		No.	No.	•			Class	
		(gene)	(protein)					
	yhfM	174	345	3497496	3498884	predicted operon	Putative Transport	
	yhfN	175	346	3498884	3499927		Putative Transport	:
	yhfO	176	347	3499890	3500339		Hypothetical,	
	,			•	••••		unclassified, unknown	
EcXA069		x	x			same operon as EcXA058		
EcXA070	ybcQ	177	348	573179	573562	predicted operon	Hypothetical, unclassified, unknown	
EcXA071	fth	178	349	2744454	2745815	predicted operon	Transport and binding proteins	
EcXA072	recJ	179	350	3034393	3036126	predicted operon	Transcription, RNA processing and degradation	
	dsbC	180	351	3036132	3036842		Cell structure	
	xerD	181	352	3036867	3037763		DNA replication, recombination, modification and repair	
EcXA073	ecpD	182	353	155461	156201	documented	·	
	htrE	183	354	152829	155426		Cell structure	
EcXA074	yciR	184	355	1342781	1344766	predicted operon	Hypothetical, unclassified, unknown	
EcXA075	sfmC	185	356	558197	558889	predicted operon	Putative chaperonin	i
	sfmD	186	357	558920	561523		Cell structure	
	sfmH	187	358	561565	562542		Cell processes (incl. adaptation, protection)	
	sfmF	188	359	562553	563068		Cell processes (incl. adaptation, protection)	
EcXA076	rim J	189	360	1124785	1125369	predicted operon	Translation, post- translational modification	
	yceH	190	361	1125380	1126027		Hypothetical, unclassified, unknown	
	mviM	191	362	1126029	1126952		Cell processes (incl. adaptation, protection)	
EcXA077	sanA	192	363	2230898	2231617	predicted		
	b2145	193	364	2231620	2231859		Hypothetical, unclassified, unknown	
EcXA078	ycgB	194	365	1234932	1236464	predicted operon	Hypothetical, unclassified, unknown	
EcXA079	yedV	195	366	2034816	2036174	predicted	Hypothetical, unclassified, unknown	
	yedW	196	367	2036174	2036893		Hypothetical, unclassified, unknown	
EcXA080		x	x			same operon as EcXA058		
EcXA081	b2107	197	368	2184800	2185318	predicted	Hypothetical, unclassified, unknown	
	ь2106	198	369	2183937	2184761		Hypothetical, unclassified, unknown	
EcXA082	hybG	199	370	3137731	3137979	documented	Energy metabolism	
	hybF	200	371	3137992			Energy metabolism	
	hybE	201	372	3138326	3138814		Energy metabolism	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number	Gene	No.	No.		3,04	0,4	Class	
		(gene)	(protein)					
	hybD	202	373	3138807	3139301		Energy metabolism	
	hybC	203	374	3139301	3141004		Energy metabolism	
	hybB	204	375	3141001	3142179		Energy metabolism	
	hybA	205	376	3142169	3143155		Energy metabolism	
EcXA083	hrpB	206	377	162060	164534		Transcription, RNA	
	•						processing and	
							degradation	
EcXA084	ы399	207	378	1461563	1462513		Hypothetical,	
							unclassified, unknown	
	ь1400	208	379	1462495	1463085		Hypothetical,	
							unclassified, unknown	
EcXA085	agaZ	209	380	3276555	3277835	predicted	Carbon compound	putative tagatose 6-
							catabolism	phosphate kinase 2
	agaV	210	381	3277822	3278331		Central intermediary	PTS system, (EIIB-
							metabolism	AGA)
	agaW	211	382	3278342	3278743		Central intermediary	PTS system (EIIC)
	-6						metabolism	(
		212	383	3278763	3279266		Central intermediary	putative N-NAG-6-
-	agaA	212	363	3416103	3217200		metabolism	phosphatedeacetylase
							·	phospinacocarciyiase
						• •		
	agaS	213	384	3279617	3280771		Central intermediary	putative tagatose-6-
							metabolism	phosphate
								aldose/ketose
								isomerase
	agaY	214	385	3280784	3281644		Central intermediary	tagatose-bisphosphate
	-						metabolism	aldotase 2
EcXA086	rpsM	215	386	3439752	3440108	documented	Translation, post-	
20721000		2	200	2 1221102	•		translational modification	
	K	216	387	3430346	3439735		Translation, post-	
	rpsK	210	301	3437340	3437133		translational modification	
				2 422 422				
	rpsD	217	388	3438692	3439312		Translation, post-	
							translational modification	
	rpoA	218	389	3437677	3438666		Translation, post-	
							translational modification	•
	rplQ	219	390	3437253	3437636		Translation, post-	٠
							translational modification	
EcXA087	ychW	220	391	2213765	2214496	predicted	Hypothetical,	
	-					-	unclassified, unknown	
	yehX	221	392	2214501	2215427		Hypothetical,	•
							unclassified, unknown	
	yehY	222	393	2215420	2216577		Hypothetical,	
		_					unclassified, unknown	
	yehZ	223	394	2216584	2217501		Hypothetical,	
D. W. 605			61	•			unclassified, unknown	
EcXA088		x	x			Same as		
						EcXAO60		
EcXA089	yadS	224	395	177662	178462	predicted	Hypothetical,	
χ.						operon	unclassified, unknown	
		•		100000			17 . 4	
	yadT	225	396	177662	178462		Hypothetical,	
	_6	224	202	170455	170162		unclassified, unknown	
<u> </u>	pfs	226	397	178455	179153			

Molecule Number	Gene	Seq ID No. (gene)	Seq ID No. (protein)	Start	Stop	Operon	Blattner Functional Class	Predicted Function
EcXA090	lpxA	227	398	202560	203348	predicted		
						operon		
	lpxB	228	399	203348	204496			
	mhB	229	400	204493	205089			RnaaseH 2
	dnaE	230	401	205126	208608			DNA pol III subunit
EcXA091	ykgE	231	402	320832	321551	predicted	Hypothetical, unclassified, unknown	
	ykgF	232	403	321562	322989		Hypothetical, unclassified, unknown	
	ykgG	233	404	322829	323677		Hypothetical, unclassified, unknown	
EcXA092	b1497	234	405	1577657	1578829	predicted	Hypothetical,	
	b1498	235	406	1578866	1580581		unclassified, unknown Hypothetical,	•
EcXA093	yohM	236	407	2183937	2184761	predicted	unclassified, unknown Hypothetical,	
	b2107	237	408	2184800	2185318		unclassified, unknown Hypothetical,	
EcXA094	yfjW	238	409	2771339	2773042	predicted	unclassified, unknown Hypothetical,	
							unclassified, unknown	
EcXA095	b2758	239	410	2879074	2880165	predicted	Hypothetical, unclassified, unknown	
EcXA096	ygcM	240	411	2890237	2890602	predicted	Hypothetical, unclassified, unknown	
	ygcN	241	412	2890650	2891951		Hypothetical,	
	b2767	242	413	2891906	2892202		unclassified, unknown Hypothetical, unclassified, unknown	
	b2768	243	414	2892219	2892794		Hypothetical, unclassified, unknown	
EcXA097	yhcB	244	415	3377820	3378224	predicted operon	Hypothetical, unclassified, unknown	
	hhoA (degQ)	245	416	3378378	3379745	predicted operon	Translation, post- translational modification	
	hhoB	246	417	3379835	3380902		Translation, post- translational modification	
EcXA098	грѕМ	247	418	3439752	3440108	documented	Translation, post- translational modification	
	rpsK	248	419	3439346	3439735		Translation, post- translational modification	
	rpsD	249	420	3438692	3439312		Translation, post- translational modification	
	гроА	250	421	3437677	3438666		Translation, post- translational modification	
	τρlQ	251	422	3437253	3437636		Translation, post- translational modification	
EcXA099		x	x			same as EcXA060		
EcXA100	rpmH	252	423	3881965	3882105	documented	Translation, post- translational modification	
	mpA	253	424	3882122	3882481		DNA replication, recombination, modification and repair	

Molecule	Gene	Seq ID	Seq ID	Start	Stop	Operon	Blattner Functional	Predicted Function
Number		No. (gene)	No. (protein)		_		Class	
EcXA101	yihK	254	425	4055987	4057762	predicted operon	Hypothetical, unclassified, unknown	
EcXA102	adi	255	426	4335832	4338102	documented	Putative regulatory proteins	biodegradative acid- induced arginine decarboxylase
	adiY	256	427	4334746	4335507		Amino acid biosynthesis and metabolism	
EcXA103	yjhB	257	428	4501566	4502843	predicted operon	Hypothetical, unclassified, unknown	
	yjhC	258	429	4502840	4503973		Hypothetical, unclassified, unknown	
EcXA104	hsdS	259	430	4577638	4579032	documented	DNA replication, recombination, modification and repair	host specificity
	hsdM	260	431	4579029	4580618		DNA replication, recombination, modification and repair	. *
EcXA105	b1357	261	432	1418389	1418685	predicted	Hypothetical, unclassified, unknown	
	ь1358	262	433	1418708	1419130		Hypothetical, unclassified, unknown	,
	ydaU	263	434	1419143	1420000		Hypothetical, unclassified, unknown	
	ь1360	264	435	1420007	1420753		Hypothetical, unclassified, unknown	,
	b1361	265	436	1420725	1421336		Hypothetical, unclassified, unknown	
	b1362	266	437	1421363	1421668		Hypothetical, unclassified, unknown	
EcXA106	ybbQ	267	438	535810	536688	predicted	Hypothetical, unclassified, unknown	+
	ybbV	268	439	536720	536998		Hypothetical, unclassified, unknown	
	ь0511	269	440	536998	538311		Hypothetical, unclassified, unknown	
EcXA107	yegM	270	441	2151891	2153285	predicted	Hypothetical, unclassified, unknown	
	yegN	271	442	2153285	2156407		Hypothetical, unclassified, unknown	•
	yegO	272	443	2156408	2159485		Hypothetical, unclassified, unknown	
	yegB	273	444	2159486	2160901		Hypothetical, unclassified, unknown	
EcXA108	yigK	274	445	4006046	4006462		Hypothetical, unclassified, unknown	
EcXA109	modA	275	446	794312	795085	documented	Transport and binding proteins	molybdate uptake
	modB	276	447	795085	795774		Transport and binding proteins	-
	modC	277	448	795777	796835		Transport and binding proteins	
EcXA110	ynaF	278	449	1433209	1433715	predicted	Hypothetical, unclassified, unknown	
	b1377	279	450	1433784	1434917	predicted	Hypothetical, unclassified, unknown	
EcXA111	recC	280	451	2957082	· 2960450	predicted	Transcription, RNA processing and	

Molecule Number	Gene	Seq ID No. (gene)	Seq ID No. (protein)	Start	Stop	Operon	Blattner Functional Class	Predicted Function
		(gene)	(protat)				degradation	
	ppdC	281	452	2960463	2960786		Other known genes	prepilin peptidase dependent protein C
	ygdB	282	453	2960771	2961136		Hypothetical, unclassified, unknown	
	ppdB	283	454	2961175	2961738		Other known genes	prepilin peptidase dependent protein B
	ppdA	284	455	2961729	2962199		Other known genes	prepilin peptidase dependent protein A
EcXA112	yrff	285	456	3524107	3526242	predicted	Hypothetical, unclassified, unknown	
	yrfG	286	457	3526262	3526975		Hypothetical, unclassified, unknown	
	yrfH	287	458	3526986	3527387		Hypothetical, unclassified, unknown	
	yrfl	288	459	3527406	3528290		Hypothetical, unclassified, unknown	
EcXA113		x	x			same as EcXA106		
EcXA114	b2350	289	460	2465875	2466237	predicted	Hypothetical, unclassified, unknown	
	b2351	290	461	2466234	2467154		Hypothetical, unclassified, unknown	
	b2352	291	462	2467151	2468482		Hypothetical,	
	b2353	292	463	2468781	2469125	predicted	unclassified, unknown Hypothetical,	
EcXA115	ygeF	293	464	2988576	2989022	predicted	unclassified, unknown Hypothetical,	
EcXA116	insB_3	294	465	289873	290376	predicted	unclassified, unknown phage, transposon, or	
	insA_3	295	466	290295	290570		plasmid phage, transposon, or	
EcXA117	rhsA	296	467	3759810	3763943	predicted	plasmid Hypothetical,	
	yibA	297	468	3763964	3763806		unclassified, unknown Hypothetical,	
	yibJ	298	469	3764848	3765549		unclassified, unknown Hypothetical, unclassified, unknown	

Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. Biological functions for genes that lie on the same operon as an identified gene have also been made. The functions for the genes of interest appear in Table II.

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The genes of interest have a variety of biological functions. For example, genes that are thought to function as transport or binding proteins, that participate in translation or post-translational modification, that are involved in carbon compound catabolism, that are thought to be enzymes,

participate in cell processes, energy metabolism and biosynthetic functions appear in Table II. Genes that are involved in cell structure, transcription, RNA processing and degradation also appear in Table II.

Several of the expression vectors contain fragments that correspond to genes of unknown function or if the function is known, it is not known whether the gene is essential. For example, EcXA056, 057, 059, 063, 064, 065, 067, 068, 070, 073, 074, 075, 076, 077, 078, 079, 081, 084, 085, 087, 089, 091, 092, 093, 094, 095, 096, 097, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 and 117 are all exogenous nucleic acid sequences that correspond to *E. coli* proteins that have no known function or where the function has not been shown to be essential or nonessential.

The present invention reports a number of novel *E. coli* genes and operons that are required for proliferation. From the list of clone sequences identified here, each was identified to be a portion of a gene in an operon required for the proliferation of *E. coli*. Cloned sequences corresponding to genes already known to be required for proliferation in *E. coli* include EcXA058, 060, 066, 069, 071, 080, 086, 088, 090, 098, 099 and 100 are exogenous nucleic acid sequences that correspond to *E. coli* genes that are known to be required for cellular proliferation. The remaining identified sequences correspond to *E. coli* genes previously undesignated as required for proliferation in the art.

An interesting observation of the present invention is that there are also several sequence fragments that correspond to *E. coli* genes that are not thought to be required for *E. coli* proliferation. Nevertheless, under the conditions described above, the antisense expression of these gene fragments causes a reduction in cell growth. This result implies that the genes corresponding to the identified sequences are actually required for proliferation or are in operons required for proliferation. Molecule Nos. corresponding to these genes are EcXA061, 062, 072, 082, 083, 104 and 116.

Following identification of the sequences of interest, these sequences were localized into operons. Since bacterial genes are expressed in a polycistronic manner, the antisense inhibition of a single gene in an operon might effect the expression of all the other genes on the operon or the genes down stream from the single gene identified. In order to determine which of the gene products in an operon are required for proliferation, each of the genes contained within an operon may be analyzed for their effect on viability as described below.

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TABLE III
Operon Boundaries

Molecule	Start	Stop
Number		
EcXA056	1168635	1169597
EcXA057	4217880	4220066
EcXA059	2776167	2780876
EcXA061	4240205	4243998
EcXA062	3958292	3960313
EcXA063	2380733	2381944
EcXA064	446039	450834
EcXA065	3869477	3872395
EcXA067	3728760	3729752
EcXA068	3497085	3500339
EcXA070	573179	573562
EcXA071	2744454	2745815
EcXA072	3034393	3037763
EcXA073	152829	156201
EcXA074	1342781	1344766
EcXA075	558197	563068
EcXA076	1124785	1126952
EcXA077	2230898	2231859
EcXA078	1234932	1236464
EcXA079	2034816	2036893
EcXA081	2183937	2185318
EcXA082	3137731	3143155
EcXA083	162060	164534
EcXA084	1461563	1463085
EcXA085	3276555	3280771
EcXA086	343 <i>7</i> 253	3440108
EcXA087	2213765	2217501
EcXA089	177662	179153
EcXA090	202560	208608
EcXA091	320832	323677
EcXA092	1577657	1580581
EcXA093	2183937	2185318
EcXA094	2771339	2773042
EcXA095	2879074	2880165
EcXA096	2890237	2892794

Molecule	Start	Stop
Number		
EcXA097	3377820	3380902
EcXA098	3437253	3438666
EcXA100	3881965	3882481
EcXA101	4055987	4057762
EcXA102	4334746	4338102
EcXA103	4501566	4503973
EcXA104	4577638	4580618
EcXA105	1418389	1421668
EcXA106	535810	538311
EcXA107	2151891	2160901
EcXA108	4006046	4006462
· EcXA109	794312	796835
EcXA110	1433209	1434917
EcXA111	2957082	2962199
EcXA112	3524107	3528290
EcXA114	2465875	2469125
EcXA115	2988576	2989022
EcXA116	289873	290570
EcXA117	3759810	3765549

EXAMPLE 5Identification of Individual Genes within an Operon Required for Proliferation

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The following example illustrates a method for determining which gene in an operon is required for proliferation. The clone insert corresponding to Molecule No. EcXA066 possesses nucleic acid sequence homology to the *E. coli* genes *rplT* and *rpml*. These genes are located in an operon containing two additional genes, *infC* and *thrS*. To determine which gene or genes in this operon are required for proliferation, each gene is selectively inactivated using homologous recombination. Gene *rplT* is the first gene to be inactivated.

Deletion inactivation of a chromosomal copy of a gene in *E. coli* can be accomplished by integrative gene replacement. The principle of this method (Hamilton, C. M., et al 1989. *J. Bacteriol.* 171: 4617-4622) is to construct a mutant allele of the targeted gene, introduce that allele into the chromosome using a conditional suicide vector, and then force the removal of the native wild type allele and vector sequences. This will replace the native gene with a desired mutation(s) but leave promoters, operators, etc. intact. Essentiality of a gene is determined either by deduction from genetic analysis or by conditional expression of a wild type copy of the targeted gene (trans complementation).

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The first step is to generate a mutant rplT allele using PCR amplification. Two sets of PCR primers are chosen to produce a copy of rplT with a large central deletion to inactivate the gene. In order to eliminate polar effects, it is desirable to construct a mutant allele comprising an in-frame deletion of most or all of the coding region of the rplT gene. Each set of PCR primers is chosen such that a region flanking the gene to be amplified is sufficiently long to allow recombination (typically at least 500 nucleotides on each side of the deletion). The targeted deletion or mutation will be contained within this fragment. To facilitate cloning of the PCR product, the PCR primers may also contain restriction endonuclease sites found in the cloning region of a conditional knockout vector such as pKO3 (Link, et al 1997 J. Bacteriol. 179 (20): 6228-6237). Suitable sites include NotI, SalI, BamHI and SmaI. The rplT gene fragments are produced using standard PCR conditions including, but not limited to, those outlined in the manufacturers directions for the Hot Start Taq PCR kit (Qiagen, Inc., Valencia, CA). The PCR reactions will produce two fragments that can be fused together. Alternatively, crossover PCR can be used to generate a desired deletion in one step (Ho, S. N., et al 1989. Gene 77: 51-59, Horton, R. M., et al 1989. Gene 77: 61-68). The mutant allele thus produced is called a "null" allele because it cannot produce a functional gene product.

The mutant allele obtained from PCR amplification is cloned into the multiple cloning site of pKO3. Directional cloning of the *rplT* null allele is not necessary. The pKO3 vector has a temperature-sensitive origin of replication derived from pSC101. Therefore, clones are propagated at the permissive temperature of 30°C. The vector also contains two selectable marker genes: one that confers resistance to chloramphenicol and another, the *Bacillus subtilis sacB* gene, that allows for counter-selection on sucrose containing growth medium. Clones that contain vector DNA with the null allele inserted are confirmed by restriction endonuclease analysis and DNA sequence analysis of isolated plasmid DNA. The plasmid containing the *rplT* null allele insert is known as a knockout plasmid.

Once the knockout plasmid has been constructed and its sequence verified, it is transformed into a Rec⁺ E. coli host cell. Transformation can be by any standard method such as electroporation. In some fraction of the transformed cells, plasmids will integrate into the E. coli chromosome by homologous recombination between the rplT null allele in the plasmid and the rplT gene in the chromosome. Transformant colonies in which such an event has occurred are readily selected by growth at the non-permissive temperature of 43°C and in the presence of choramphenicol. At this temperature, the plasmid will not replicate as an episome and will be lost from cells as they grow and divide. These cells are no longer resistant to chloramphenicol and will not grow when it is present. However, cells in which the knockout plasmid has integrated into the E. coli chromosome remain resistant to chloramphenicol and propagate.

Cells containing integrated knock-out plasmids are usually the result of a single crossover event that creates a tandem repeat of the mutant and native wild type alleles of rplT separated by the

vector sequences. A consequence of this is that rplT will still be expressed in these cells. In order to determine if the gene is essential for growth, the wild type copy must be removed. This is accomplished by selecting for plasmid excision, a process in which homologous recombination between the two alleles results in looping out of the plasmid sequences. Cells that have undergone such an excision event and have lost plasmid sequences including sacB gene are selected for by addition of sucrose to the medium. The sacB gene product converts sucrose to a toxic molecule. Thus counter selection with sucrose ensures that plasmid sequences are no longer present in the cell. Loss of plasmid sequences is further confirmed by testing for sensitivity to chloramphenicol (loss of the chloramphenicol resistance gene). The latter test is important because occasionally a mutation in the sacB gene can occur resulting in a loss of sacB function with no effect on plasmid replication (Link, et. al., 1997 J. Bacteriol. 179 (20): 6228-6237). These artifact clones retain plasmid sequences and are therefore still resistant to chloramphenicol.

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In the process of plasmid excision, one of the two rplT alleles is lost from the chromosome along with the plasmid DNA. In general, it is equally likely that the null allele or the wild type allele will be lost. Therefore, if the rplT gene is not essential, half of the clones obtained in this experiment will have the wild type allele on the chromosome and half will have the null allele. However, if the rplT gene is essential, cells containing the null allele will not be obtained as a single copy of the null allele would be lethal.

To determine the essentiality of rplT, a statistically significant number of the resulting clones, at least 20, are analyzed by PCR amplification of the rplT gene. Since the null allele is missing a significant portion of the rplT gene, its PCR product is significantly shorter than that of the wild type gene and the two are readily distinguished by gel electrophoretic analysis. The PCR products may also be subjected to sequence determination for further confirmation by methods well known to those in the art.

The above experiment is generally adequate for determining the essentiality of a gene such as rplT. However, it may be necessary or desirable to more directly confirm the essentiality of the gene. There are several methods by which this can be accomplished. In general, these involve three steps: 1) construction of an episome containing a wild type allele, 2) isolation of clones containing a single chromosomal copy of the mutant null allele as described above but in the presence of the episomal wild type allele, and then 3) determining if the cells survive when the expression of the episomal allele is shut off. In this case, the trans copy of wild type rplT is made by PCR cloning of the entire coding region of rplT and inserting it in the sense orientation downstream of an inducible promoter such as the E. coli lac promoter. Transcription of this allele of rplT will be induced in the presence of IPTG which inactivates the lac repressor. Under IPTG induction rplT protein will be expressed as long as the recombinant gene also possesses a ribosomal binding site, also known as a "Shine-Dalgamo Sequence". The trans copy of rplT is cloned on a plasmid that is compatible with pSC101. Compatible vectors include p15A, pBR322, and the pUC

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plasmids, among others. Replication of the compatible plasmid will not be temperature-sensitive. The entire process of integrating the null allele of rplT and subsequent plasmid excision is carried out in the presence of IPTG to ensure the expression of functional rplT protein is maintained throughout. After the null rplT allele is confirmed as integrated on the chromosome in place of the wild type rplT allele, then IPTG is withdrawn and expression of functional rplT protein shut off. If the rplT gene is essential, cells will cease to proliferate under these conditions. However, if the rplT gene is not essential, cells will continue to proliferate under these conditions. In this experiment, essentiality is determined by conditional expression of a wild type copy of the gene rather than inability to obtain the intended chromosomal disruption.

An advantage of this method over some other gene disruption techniques is that the targeted gene can be deleted or mutated without the introduction of large segments of foreign DNA. Therefore, polar effects on downstream genes are eliminated or minimized. There are methods described to introduce inducible promoters upstream of potential essential bacterial genes. However in such cases, polarity from multiple transcription start points can be a problem. One way of preventing this is to insert a gene disruption cassette that contains strong transcriptional terminators upstream of the integrated inducible promoter (Zhang, Y, and Cronan, J. E. 1996 J. Bacteriol. 178 (12): 3614-3620). The described techniques will all be familiar to one of ordinary skill in the art.

Following the analysis of the *rplT* gene, the other genes of the operon are investigated to determine if they are required for proliferation.

EXAMPLE 6

Expression of the Proteins Encoded by Genes Identified as Required for E. coli Proliferation

The following is provided as one exemplary method to express the proliferation-required proteins encoded by the identified sequences described above. First, the initiation and termination codons for the gene are identified. If desired, methods for improving translation or expression of the protein are well known in the art. For example, if the nucleic acid encoding the polypeptide to be expressed lacks a methionine codon to serve as the initiation site, a strong Shine-Delgamo sequence, or a stop codon, these sequences can be added. Similarly, if the identified nucleic acid sequence lacks a transcription termination signal, this sequence can be added to the construct by, for example, splicing out such a sequence from an appropriate donor sequence. In addition, the coding sequence may be operably linked to a strong promoter or an inducible promoter if desired. The identified nucleic acid sequence or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial expression vector or genome using oligonucleotide primers complementary to the identified nucleic acid sequence or portion thereof and containing restriction endonuclease sequences for *Ncol* incorporated into the 5' primer and *Bgl*II at the 5' end of the corresponding 3'-primer, taking care to ensure that the identified nucleic acid sequence is positioned in frame with the termination signal. The

purified fragment obtained from the resulting PCR reaction is digested with *NcoI* and *BgIII*, purified and ligated to an expression vector.

The ligated product is transformed into DH5 α or some other *E. coli* strain suitable for the over expression of potential proteins. Transformation protocols are well known in the art. For example, transformation protocols are described in: Current Protocols in Molecular Biology, Vol. 1, Unit 1.8, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Positive transformants are selected after growing the transformed cells on plates containing 50-100 µg/ml Ampicillin (Sigma, St. Louis, Missouri). In one embodiment, the expressed protein is held in the cytoplasm of the host organism. In an alternate embodiment, the expressed protein is released into the culture medium. In still another alternative, the expressed protein can be sequestered in the periplasmic space and liberated therefrom using any one of a number of cell lysis techniques known in the art. For example, the osmotic shock cell lysis method described in Chapter 16 of Current Protocols in Molecular Biology, Vol. 2, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Each of these procedures can be used to express a proliferation-required protein.

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Expressed proteins, whether in the culture medium or liberated from the periplasmic space or the cytoplasm, are then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, standard chromatography, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and HPLC. Alternatively, the secreted protein can be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment. The purity of the protein product obtained can be assessed using techniques such as Coomassie or silver staining or using antibodies against the control protein. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest can be generated using synthetic peptides using methods well known in the art. See, Antibodies: A Laboratory Manual, (Harlow and Lane, Eds.) Cold Spring Harbor Laboratory (1988). For example, 15-mer peptides having a sequence encoded by the appropriate identified gene sequence of interest or portion thereof can be chemically synthesized. The synthetic peptides are injected into mice to generate antibodies to the polypeptide encoded by the identified nucleic acid sequence of interest or portion thereof. Alternatively, samples of the protein expressed from the expression vectors discussed above can be purified and subjected to amino acid sequencing analysis to confirm the identity of the recombinantly expressed protein and subsequently used to raise antibodies. An Example describing in detail the generation of monoclonal and polyclonal antibodies appears in Example 7.

The protein encoded by the identified nucleic acid sequence of interest or portion thereof can be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted

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protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques. These procedures are well known in the art.

In an alternative protein purification scheme, the identified nucleic acid sequence of interest or portion thereof can be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the identified nucleic acid sequence of interest or portion thereof is inserted in-frame with the gene encoding the other half of the chimera. The other half of the chimera can be maltose binding protein (MBP) or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to MBP or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites can be engineered between the MBP gene or the nickel binding polypeptide and the identified expected gene of interest, or portion thereof. Thus, the two polypeptides of the chimera can be separated from one another by protease digestion.

One useful expression vector for generating maltose binding protein fusion proteins is pMAL (New England Biolabs), which encodes the *malE* gene. In the pMal protein fusion system, the cloned gene is inserted into a pMal vector downstream from the *malE* gene. This results in the expression of an MBP-fusion protein. The fusion protein is purified by affinity chromatography. These techniques as described are well known to those skilled in the art of molecular biology.

EXAMPLE 7

Production of an Antibody to an isolated E. coli Protein

Substantially pure protein or polypeptide is isolated from the transformed cells as described in Example 6. The concentration of protein in the final preparation is adjusted, for example, by concentration on a 10,000 molecular weight cut off AMICON filter device (Millipore, Bedförd, MA), to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or any of the well-known derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as ELISA, as described by Engvall, E., "Enzyme immunoassay ELISA and EMIT," Meth.

Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

Polyclonal Antibody Production by Immunization

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Polyclonal antiserum containing antibodies to heterogeneous epitopes of a single protein or a peptide can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than larger molecules and can require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: **Handbook of Experimental Immunology** D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: **Manual of Clinical Immunology**, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies can also be used in therapeutic compositions for killing bacterial cells expressing the protein.

EXAMPLE 8

Screening Chemical Libraries

A. Protein-Based Assays

Having isolated and expressed bacterial proteins shown to be required for bacterial proliferation, the present invention further contemplates the use of these expressed proteins in assays to screen libraries of compounds for potential drug candidates. The generation of chemical libraries is well known in the art. For example combinatorial chemistry can be used to generate a library of compounds to be screened in the assays described herein. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological

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synthesis by combining a number of chemical "building blocks" reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining amino acids in every possible combination to yield peptides of a given length. Millions of chemical compounds theoretically can be synthesized through such combinatorial mixings of chemical building blocks. For example, one commentator observed that the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery, Background and Peptide Combinatorial Libraries," Journal of Medicinal Chemistry, Vol. 37, No. 9, 1233-1250 (1994). Other chemical libraries known to those in the art may also be used, including natural product libraries.

Once generated, combinatorial libraries can be screened for compounds that possess desirable biological properties. For example, compounds which may be useful as drugs or to develop drugs would likely have the ability to bind to the target protein identified, expressed and purified as discussed above. Further, if the identified target protein is an enzyme, candidate compounds would likely interfere with the enzymatic properties of the target protein. Any enzyme can be a target protein. For example, the enzymatic function of a target protein can be to serve as a protease, nuclease, phosphatase, dehydrogenase, transporter protein, transcriptional enzyme, and any other type of enzyme known or unknown. Thus, the present invention contemplates using the protein products described above to screen combinatorial and other chemical libraries.

Those in the art will appreciate that a number of techniques exist for characterizing target proteins in order to identify molecules useful for the discovery and development of therapeutics. For example, some techniques involve the generation and use of small peptides to probe and analyze target proteins both biochemically and genetically in order to identify and develop drug leads. Such techniques include the methods described in PCT publications No. WO9935494, WO9819162, WO9954728.

In another example, the target protein is a serine protease and the substrate of the enzyme is known. The present example is directed towards the analysis of libraries of compounds to identify compounds that function as inhibitors of the target enzyme. First, a library of small molecules is generated using methods of combinatorial library formation well known in the art. U.S. Patent NOs. 5,463,564 and 5,574, 656, to Agrafiotis, et al., entitled "System and Method of Automatically Generating Chemical Compound with Desired Properties," are two such teachings. Then the library compounds are screened to identify library compounds that possess desired structural and functional properties. U.S. Patent No. 5,684,711 also discusses a method for screening libraries.

To illustrate the screening process, the combined target and chemical compounds of the library are exposed to and permitted to interact with the purified enzyme. A labeled substrate is added to the incubation. The label on the substrate is such that a detectable signal is emitted from metabolized substrate molecules. The emission of this signal permits one to measure the effect of the combinatorial

library compounds on the enzymatic activity of target enzymes. The characteristics of each library compound is encoded so that compounds demonstrating activity against the enzyme can be analyzed and features common to the various compounds identified can be isolated and combined into future iterations of libraries.

Once a library of compounds is screened, subsequent libraries are generated using those chemical building blocks that possess the features shown in the first round of screen to have activity against the target enzyme. Using this method, subsequent iterations of candidate compounds will possess more and more of those structural and functional features required to inhibit the function of the target enzyme, until a group of enzyme inhibitors with high specificity for the enzyme can be found. These compounds can then be further tested for their safety and efficacy as antibiotics for use in mammals.

It will be readily appreciated that this particular screening methodology is exemplary only. Other methods are well known to those skilled in the art. For example, a wide variety of screening techniques are known for a large number of naturally-occurring targets when the biochemical function of the target protein is known.

B. Cell Based Assays

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Current cell-based assays used to identify or to characterize compounds for drug discovery and development frequently depend on detecting the ability of a test compound to inhibit the activity of a target molecule located within a cell or located on the surface of a cell. Most often such target molecules are proteins such as enzymes, receptors and the like. However, target molecules may also include other molecules such as DNAs, lipids, carbohydrates and RNAs including messenger RNAs, ribosomal RNAs, tRNAs and the like. A number of highly sensitive cell-based assay methods are available to those of skill in the art to detect binding and interaction of test compounds with specific target molecules. However, these methods are generally not highly effective when the test compound binds to or otherwise interacts with its target molecule with moderate or low affinity. In addition, the target molecule may not be readily accessible to a test compound in solution, such as when the target molecule is located inside the cell or within a cellular compartment such as the periplasm of a bacterial cell. Thus, current cell-based assay methods are limited in that they are not effective in identifying or characterizing compounds that interact with their targets with moderate to low affinity or compounds that interact with targets that are not readily accessible.

Cell-based assays methods of the present invention have substantial advantages over current cell-based assays practiced in the art. These advantages derive from the use of sensitized cells in which the level or activity of a proliferation-required gene product (the target molecule) has been specifically reduced to the point where the presence or absence of its function becomes a rate-determining step for cellular proliferation. Bacterial, fungal, plant, or animal cells can all be used with the present method. Such sensitized cells become much more sensitive to compounds that are

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active against the affected target molecule. Thus, cell-based assays of the present invention are capable of detecting compounds exhibiting low or moderate potency against the target molecule of interest because such compounds are substantially more potent on sensitized cells than on non-sensitized cells. The affect may be such that a test compound may be two to several times more potent, at least 10 times more potent or even at least 100 times more potent when tested on the sensitized cells as compared to the non-sensitized cells.

Due in part to the increased appearance of antibiotic resistance in pathogenic microorganisms and to the significant side-effects associated with some currently used antibiotics, novel antibiotics acting at new targets are highly sought after in the art. Yet, another limitation in the current art related to cell-based assays is the problem of identifying hits against the same kinds of target molecules in the same limited set of biological pathways over and over again. This may occur when compounds acting at such new targets are discarded, ignored or fail to be detected because compounds acting at the "old" targets are encountered more frequently and are more potent than compounds acting at the new targets. As a result, the majority of antibiotics in use currently interact with a relatively small number of target molecules within an even more limited set of biological pathways.

The use of sensitized cells of the current invention provides a solution to the above problem in two ways. First, desired compounds acting at a target of interest, whether a new target or a previously known but poorly exploited target, can now be detected above the "noise" of compounds acting at the "old" targets due to the specific and substantial increase in potency of such desired compounds when tested on the sensitized cells of the current invention. Second, the methods used to sensitize cells to compounds acting at a target of interest may also sensitize these cells to compounds acting at other target molecules within the same biological pathway. For example, expression of an antisense molecule to a gene encoding a ribosomal protein is expected to sensitize the cell to compounds acting at that ribosomal protein and may also sensitize the cells to compounds acting at any of the ribosomal components (proteins or rRNA) or even to compounds acting at any target which is part of the protein synthesis pathway. Thus an important advantage of the present invention is the ability to reveal new targets and pathways that were previously not readily accessible to drug discovery methods.

Sensitized cells of the present invention are prepared by reducing the activity or level of a target molecule. The target molecule may be a gene product, such as an RNA or polypeptide produced from the proliferation-required nucleic acids described herein. Alternatively, the target may be a gene product such as an RNA or polypeptide which is produced form a sequence within the same operon as the proliferation-required nucleic acids described herein. In addition, the target may be an RNA or polypeptide in the same biological pathway as the proliferation-required nucleic acids described herein. Such biological pathways include, but are not limited to, enzymatic,

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biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such the cell wall.

Current methods employed in the arts of medicinal and combinatorial chemistries are able to make use of structure-activity relationship information derived from testing compounds in various biological assays including direct binding assays and cell-based assays. Occasionally compounds are directly identified in such assays that are sufficiently potent to be developed as drugs. More often, initial hit compounds exhibit moderate or low potency. Once a hit compound is identified with low or moderate potency, directed libraries of compounds are synthesized and tested in order to identify more potent leads. Generally these directed libraries are combinatorial chemical libraries consisting of compounds with structures related to the hit compound but containing systematic variations including additions, subtractions and substitutions of various structural features. When tested for activity against the target molecule, structural features are identified that either alone or in combination with other features enhance or reduce activity. This information is used to design subsequent directed libraries containing compounds with enhanced activity against the target molecule. After one or several iterations of this process, compounds with substantially increased activity against the target molecule are identified and may be further developed as drugs. This process is facilitated by use of the sensitized cells of the present invention since compounds acting at the selected targets exhibit increased potency in such cell-based assays, thus; more compounds can now be characterized providing more useful information than would be obtained otherwise.

Thus, it is now possible using cell-based assays of the present invention to identify or characterize compounds that previously would not have been readily identified or characterized including compounds that act at targets that previously were not readily exploited using cell-based assays. The process of evolving potent drug leads from initial hit compounds is also substantially improved by the cell-based assays of the present invention because, for the same number of test compounds, more structure-function relationship information is likely to be revealed.

The method of sensitizing a cell entails selecting a suitable gene or operon. A suitable gene or operon is one whose expression is required for the proliferation of the cell to be sensitized. The next step is to introduce into the cells to be sensitized, an antisense RNA capable of hybridizing to the suitable gene or operon or to the RNA encoded by the suitable gene or operon. Introduction of the antisense RNA can be in the form of an expression vector in which antisense RNA is produced under the control of an inducible promoter. The amount of antisense RNA produced is limited by varying the inducer concentration to which the cell is exposed and thereby varying the activity of the promoter driving transcription of the antisense RNA. Thus, cells are sensitized by exposing them to an inducer concentration that results in a sub-lethal level of antisense RNA expression.

In one embodiment of the cell-based assays, the identified exogenous E. coli nucleotide sequences of the present invention are used to inhibit the production of a proliferation-required

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protein. Expression vectors producing antisense RNA against identified genes required for proliferation are used to limit the concentration of a proliferation-required protein without severly inhibiting growth. To achieve that goal, a growth inhibition dose curve of inducer is calculated by plotting various doses of inducer against the corresponding growth inhibition caused by the antisense expression. From this curve, various percentages of antisense induced growth inhibition, from 1 to 100% can be determined. If the promoter contained in the expression vector contains a lac operator the transcription is regulated by lac repressor and expression from the promoer is inducible with IPTG. For example, the highest concentration of the inducer IPTG that does not reduce the growth rate (0% growth inhibition) can be predicted from the curve. Cellular proliferation can be monitored by growth medium turbidity via OD measurements. In another example, the concentration of inducer that reduces growth by 25% can be predicted from the curve. In still another example, a concentration of inducer that reduces growth by 50% can be calculated. Additional parameters such as colony forming units (cfu) can be used to measure cellular viability.

Cells to be assayed are exposed to the above-determined concentrations of inducer. The presence of the inducer at this sub-lethal concentration reduces the amount of the proliferation required gene product to a low amount in the cell that will limit but not prevent growth. Cells grown in the presence of this concentration of inducer are therefore specifically more sensitive to inhibitors of the proliferation-required protein or RNA of interest or to inhibitors of proteins or RNAs in the same biological pathway as the proliferation-required protein or RNA of interest but not to inhibitors of unrelated proteins or RNAs.

Cells pretreated with sub-inhibitory concentrations of inducer and thus containing a reduced amount of proliferation-required target gene product are then used to screen for compounds that reduce cell growth. The sub-lethal concentration of inducer may be any concentration consistent with the intended use of the assay to identify candidate compounds to which the cells are more sensitive. For example, the sub-lethal concentration of the inducer may be such that growth inhibition is at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60% at least about 75%, 90%, 95% or more. Cells which are pre-sensitized using the preceding method are more sensitive to inhibitors of the target protein because these cells contain less target protein to be inhibited than do wild-type cells.

In another embodiment of the cell based assays of the present invention, the level or activity of a proliferation required gene product is reduced using a mutation, such as a temperature sensitive mutation, in the proliferation-required sequence and an antisense nucleic acid against the proliferation-required sequence. Growing the cells at an intermediate temperature between the permissive and restrictive temperatures of the temperature sensitive mutant where the mutation is in a proliferation-required gene produces cells with reduced activity of the proliferation-required gene product. The antisense RNA directed against the proliferation-required sequence further reduces

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the activity of the proliferation required gene product. Drugs that may not have been found using either the temperature sensitive mutation or the antisense nucleic acid alone may be identified by determining whether cells in which expression of the antisense nucleic acid has been induced and which are grown at a temperature between the permissive temperature and the restrictive temperature are substantially more sensitive to a test compound than cells in which expression of the antisense nucleic acid has not been induced and which are grown at a permissive temperature. Also drugs found previously from either the antisense nucleic acid alone or the temperature sensitive mutation alone may have a different sensitivity profile when used in cells combining the two approaches, and that sensitivity profile may indicate a more specific action of the drug in inhibiting one or more activities of the gene product.

Temperature sensitive mutations may be located at different sites within the gene and correspond to different domains of the protein. For example, the dnaB gene of Escherichia coli encodes the replication fork DNA helicase. DnaB has several domains, including domains for oligomerization, ATP hydrolysis, DNA binding, interaction with primase, interaction with DnaC, and interaction with DnaA [(Biswas, E.E. and Biswas, S.B. 1999. Mechanism and DnaB helicase of Escherichia coli: structural domains involved in ATP hydrolysis, DNA binding, and oligomerization. Biochem. 38:10919-10928; Hiasa, H. and Marians, K.J. 1999. Initiation of bidirectional replication at the chromosomal origin is directed by the interaction between helicase and primase. J. Biol. Chem. 274:27244-27248; San Martin, C., Radermacher, M., Wolpensinger, B., Engel, A., Miles, C.S., Dixon, N.E., and Carazo, J.M. 1998. Three-dimensional reconstructions from cryoelectron microscopy images reveal an intimate complex between helicase DnaB and its loading partner DnaC. Structure 6:501-9; Sutton, M.D., Carr, K.M., Vicente, M., and Kaguni, J.M. 1998. Escherichia coli DnaA protein. The N-terminal domain and loading of DnaB helicase at the E. coli chromosomal. J. Biol. Chem. 273:34255-62.)]. Temperature sensitive mutations in different domains of DnaB confer different phenotypes at the restrictive temperature, which include either an abrupt stop or slow stop in DNA replication with or without DNA breakdown (Wechsler, J.A. and Gross, J.D. 1971. Escherichia coli mutants temperature-sensitive for DNA synthesis. Mol. Gen. Genetics 113:273-284) and termination of growth or cell death. Combining the use of temperature sensitive mutations in the dnaB gene that cause cell death at the restrictive temperature with an antisense to the dnaB gene could lead to the discovery of very specific and effective inhibitors of one or a subset of activities exhibited by DnaB.

When screening for antimicrobial agents against a gene product required for proliferation, growth inhibition of cells containing a limiting amount of that proliferation-required gene product can be assayed. Growth inhibition can be measured by directly comparing the amount of growth, measured by the optical density of the growth medium, between an experimental sample and a control sample. Alternative methods for assaying cell proliferation include measuring green

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used for comparison.

fluorescent protein (GFP) reporter construct emissions, various enzymatic activity assays, and other methods well known in the art.

It will be appreciated that the above method may be performed in solid phase, liquid phase or a combination of the two. For example, cells grown on nutrient agar containing the inducer of the antisense construct may be exposed to compounds spotted onto the agar surface. A compound's effect may be judged from the diameter of the resulting killing zone, the area around the compound application point in which cells do not grow. Multiple compounds may be transferred to agar plates and simultaneously tested using automated and semi-automated equipment including but not restricted to multi-channel pipettes (for example the Beckman Multimek) and multi-channel spotters (for example the Genomic Solutions Flexys). In this way multiple plates and thousands to millions of compounds may be tested per day.

The compounds may also be tested entirely in liquid phase using microtiter plates as described below. Liquid phase screening may be performed in microtiter plates containing 96, 384, 1536 or more wells per microtiter plate to screen multiple plates and thousands to millions of compounds per day. Automated and semi-automated equipment may be used for addition of reagents (for example cells and compounds) and determination of cell density.

EXAMPLE 9

Cell Based Assay Using Antisense Complementary to Genes Encoding Ribosomal Proteins

The effectiveness of the above cell based assay was validated using constructs expressing antisense RNA to the proliferation required E. coli genes rplL, rplJ, and rplW encoding ribosomal proteins L7/L12, L10 and L23 respectively. These proteins are part of the protein synthesis apparatus of the cell and as such are required for proliferation. These constructs were used to test the effect of antisense expression on cell sensitivity to antibiotics known to bind to the ribosome and thereby inhibit protein synthesis. Constructs expressing antisense RNA to several other genes (elaD, visC, yohH, and atpE/B), the products of which are not involved in protein synthesis were

First pLex5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)) expression vectors containing antisense constructs to either *rplW* or to *elaD* were introduced into separate *E. coli* cell populations. Vector introduction is a technique well known to those of ordinary skill in the art. The expression vectors of this example contain IPTG inducible promoters that drive the expression of the antisense RNA in the presence of the inducer. However, those skilled in the art will appreciate that other inducible promoters may also be used. Suitable expression vectors are also well known in the art. The *E. coli* antisense clones encoding ribosomal proteins L7/L12, L10 and L23 were used to test the effect of antisense expression on cell sensitivity to the antibiotics known to bind to these proteins. First, expression vectors containing antisense to either the genes encoding L7/L12 and L10 or L23 were introduced into separate *E. coli* cell populations.

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The cell populations were exposed to a range of IPTG concentrations in liquid medium to obtain the growth inhibitory dose curve for each clone (Fig. 1). First, seed cultures were grown to a particular turbidity that is measured by the optical density (OD) of the growth solution. The OD of the solution is directly related to the number of bacterial cells contained therein. Subsequently, sixteen 200 ul liquid medium cultures were grown in a 96 well microtiter plate at 37 C with a range of IPTG concentrations in duplicate two-fold serial dilutions from 1600 uM to 12.5 uM (final concentration). Additionally, control cells were grown in duplicate without IPTG. These cultures were started from equal amounts of cells derived from the same initial seed culture of a clone of interest. The cells were grown for up to 15 hours and the extent of growth was determined by measuring the optical density of the cultures at 600 nm. When the control culture reached mid-log phase the percent growth of the control for each of the IPTG containing cultures was plotted against the log concentrations of IPTG to produce a growth inhibitory dose response curve for the IPTG. The concentration of IPTG that inhibits cell growth to 50% (IC₅₀) as compared to the 0 mM IPTG control (0% growth inhibition) was then calculated from the curve. Under these conditions, an amount of antisense RNA was produced that reduced the expression levels of rplW and elaD to a degree such that growth was inhibited by 50%.

Alternative methods of measuring growth are also contemplated. Examples of these methods include measurements of proteins, the expression of which is engineered into the cells being tested and can readily be measured. Examples of such proteins include green fluorescent protein (GFP) and various enzymes.

Cells were pretreated with the selected concentration of IPTG and then used to test the sensitivity of cell populations to tetracycline, erythromycin and other protein synthesis inhibitors. Figure 2 is an IPTG dose response curve in E. coli transformed with an IPTG-inducible plasmid containing either an antisense clone to the E. coli ribosomal protein rplW (AS-rplW) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the elaD (AS-elaD) gene which is not known to be involved in protein synthesis and which is also essential An example of a tetracycline dose response curve is for proliferation. shown in Figures 2A and 2B for the rplW and elaD genes, respectively. Cells were grown to log phase and then diluted into media alone or media containing IPTG at concentrations which give 20% and 50% growth inhibition as determined by IPTG dose response curves. After 2.5 hours, the cells were diluted to a final OD600 of 0.002 into 96 well plates containing (1) +/- IPTG at the same concentrations used for the 2.5 hour pre-incubation; and (2) serial two-fold dilutions of tetracycline such that the final concentrations of tetracycline range from 1 µg/ml to 15.6 ng/ml and 0 µg/ml. The 96 well plates were incubated at 37°C and the OD600 was read by a plate reader every 5 minutes for up to 15 hours. For each IPTG concentration and the no IPTG control, tetracycline dose response curves were determined when the control (absence of tetracycline) reached 0.1 OD600. To compare tetracycline sensitivity with and without IPTG, tetracycline IC50s were

determined from the dose response curves (Figs. 3A-B). Cells with reduced levels of L23 (rplW) showed increased sensitivity to tetracycline (Fig. 2A) as compared to cells with reduced levels of elaD (Fig. 2B). Figure 3 shows a summary bar chart in which the ratios of tetracycline IC_{50s} determined in the presence of IPTG which gives 50% growth inhibition versus tetracycline IC_{50s} determined without IPTG (fold increase in tetracycline sensitivity) were plotted. Cells with reduced levels of either L7/L12 (genes rplL, rplJ) or L23 (rplW) showed increased sensitivity to tetracycline (Fig. 3). Cells expressing antisense to genes not known to be involved in protein synthesis (atpB/E, visC, elaD, yohH) did not show the same increased sensitivity to tetracycline, validating the specificity of this assay (Fig. 3).

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In addition to the above, it has been observed in initial experiments that clones expressing antisense RNA to genes involved in protein synthesis (including genes encoding ribosomal proteins L7/L12 & L10, L7/L12 alone, L22, and L18, as well as genes encoding rRNA and Elongation Factor G) have increased sensitivity to the macrolide, erythromycin, whereas clones expressing antisense to the non-protein synthesis genes *elaD*, *atpB/E* and *visC* do not. Furthermore, the clone expressing antisense to *rplL* and *rplJ* does not show increased sensitivity to nalidixic acid and ofloxacin, antibiotics which do not inhibit protein synthesis.

The results with the ribosomal protein genes rplL, rplJ, and rplW as well as the initial results using various other antisense clones and antibiotics show that limiting the concentration of an antibiotic target makes cells more sensitive to the antimicrobial agents that specifically interact with that protein. The results also show that these cells are sensitized to antimicrobial agents that inhibit the overall function in which the protein target is involved but are not sensitized to antimicrobial agents that inhibit other functions.

The cell based assay described above may also be used to identify the biological pathway in which a proliferation-required nucleic acid or its gene product lies. In such methods, cells expressing a sub-lethal level of antisense to a target proliferation-required nucleic acid and control cells in which expression of the antisense has not been induced are contacted with a panel of antibiotics known to act in various pathways. If the antibiotic acts in the pathway in which the target proliferation-required nucleic acid or its gene product lies, cells in which expression of the antisense has been induced will be more sensitive to the antibiotic than cells in which expression of the antisense has not been induced.

As a control, the results of the assay may be confirmed by contacting a panel of cells expressing antisense nucleic acids to many different proliferation-required genes including the target proliferation-required gene. If the antibiotic is acting specifically, heightened sensitivity to the antibiotic will be observed only in the cells expressing antisense to a target proliferation-required gene (or cells expressing antisense to other proliferation-required genes in the same pathway as the target proliferation-required gene) but will not be observed generally in all cells expressing antisense to proliferation-required genes.

Similarly, the above method may be used to determine the pathway on which a test compound, such as a test antibiotic acts. A panel of cells, each of which expresses antisense to a proliferation-required nucleic acid in a known pathway, is contacted with a compound for which it is desired to determine the pathway on which it acts. The sensitivity of the panel of cells to the test compound is determined in cells in which expression of the antisense has been induced and in control cells in which expression of the antisense has not been induced. If the test compound acts on the pathway on which an antisense nucleic acid acts, cells in which expression of the antisense has been induced will be more sensitive to the compound than cells in which expression of the antisense has not been induced. In addition, control cells in which expression of antisense to proliferation-required genes in other pathways has been induced will not exhibit heightened sensitivity to the compound. In this way, the pathway on which the test compound acts may be determined.

The Example below provides one method for performing such assays.

EXAMPLE 10

Identification of the Pathway in which a Proliferation-Required

Gene Lies or the Pathway on which an Antibiotic Acts

A. Preparation of Bacterial Stocks for Assay

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To provide a consistent source of cells to screen, frozen stocks of host bacteria containing the desired antisense construct are prepared using standard microbiological techniques. For example, a single clone of the organism can be isolated by streaking out a sample of the original stock onto an agar plate containing nutrients for cell growth and an antibiotic for which the antisense construct contains a gene which confers resistance. After overnight growth an isolated colony is picked from the plate with a sterile needle and transferred to an appropriate liquid growth media containing the antibiotic required for maintenance of the plasmid. The cells are incubated at 30°C to 37°C with vigorous shaking for 4 to 6 hours to yield a culture in exponential growth. Sterile glycerol is added to 15% (volume to volume) and 100µL to 500 µL aliquots are distributed into sterile cryotubes, snap frozen in liquid nitrogen, and stored at -80°C for future assays.

B. Growth of Bacteria for Use in the Assay

A day prior to an assay, a stock vial is removed from the freezer, rapidly thawed (37°C water bath) and a loop of culture is streaked out on an agar plate containing nutrients for cell growth and an antibiotic to which the antisense construct confers resistance. After overnight growth at 37°C, ten randomly chosen, isolated colonies are transferred from the plate (sterile inoculum loop) to a sterile tube containing 5 mL of LB medium containing the antibiotic to which the antisense vector confers resistance. After vigorous mixing to form a homogeneous cell suspension, the optical density of the suspension is measured at 600 nm (OD600) and if necessary an aliquot of the suspension is diluted into a second tube of 5 mL, sterile, LB medium plus antibiotic to achieve an

 $OD600 \le 0.02$ absorbance units. The culture is then incubated at 37° C for 1-2 hrs with shaking until the OD600 reaches OD 0.2 – 0.3. At this point the cells are ready to be used in the assay.

5 C. Selection of Media to be Used in Assay

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Two fold dilution series of the inducer are generated in culture media containing the appropriate antibiotic for maintenance of the antisense construct. Several media are tested side by side and three to four wells are used to evaluate the effects of the inducer at each concentration in each media. For example, M9 minimal media, LB broth, TBD broth and Muller-Hinton media may be tested with the inducer IPTG at the following concentrations, 50 µM, 100 µM, 200 µM, 400 µM, 600 µM, 800 µM and 1000 µM. Equal volumes of test media-inducer and cells are added to the wells of a 384 well microtiter plate and mixed. The cells are prepared as described above and diluted 1:100 in the appropriate media containing the test antibiotic immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells of each media that do not contain inducer, for example 0 µM IPTG. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of inducer is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without inducer. The medium yielding greatest sensitivity to inducer is selected for use in the assays described below.

D. Measurement of Test Antibiotic Sensitivity in the Absence of Antisense Construct Induction

Two-fold dilution series of antibiotics of known mechanism of action are generated in the culture media selected for further assay development that has been supplemented with the antibiotic used to maintain the construct. A panel of test antibiotics known to act on different pathways is tested side by side with three to four wells being used to evaluate the effect of a test antibiotic on cell growth at each concentration. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the media selected for assay development supplemented with the antibiotic required to maintain the antisense construct and are diluted 1:100 in identical media immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells that contain the solvent used to dissolve the antibiotics but no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC50 value for each antibiotic.

E. Measurement of Test Antibiotic Sensitivity in the Presence of Antisense Construct Inducer

The culture media selected for use in the assay is supplemented with inducer at concentrations shown to inhibit cell growth by 50 and 80% as described above and the antibiotic used to maintain the construct. Two fold dilution series of the panel of test antibiotics used above are generated in each of these media. Several antibiotics are tested side by side with three to four wells being used to evaluate the effects of an antibiotic on cell growth at each concentration, in each media. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter. plate and mixed. Cells are prepared as described above using the media selected for use in the assay supplemented with the antibiotic required to maintain the antisense construct. The cells are diluted 1:100 into two 50 mL aliquots of identical media containing concentrations of inducer that have been shown to inhibit cell growth by 50% and 80 % respectively and incubated at 37°C with shaking for 2.5 hours. Immediately prior to addition to the microtiter plate wells, the cultures are adjusted to an appropriate OD₆₀₀ (typically 0.002) by dilution into warm (37°C) sterile media supplemented with identical concentrations of the inducer and antibiotic used to maintain the antisense construct. For a control, cells are also added to several wells that contain solvent used to dissolve test antibiotics but which contain no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC₅₀ value for each antibiotic.

F. Determining the Specificity of the Test Antibiotics

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A comparison of the IC₅₀s generated by antibiotics of known mechanism of action under antisense induced and non-induced conditions allows the pathway in which a proliferation-required nucleic acid lies to be identified. If cells expressing an antisense nucleic acid against a proliferation-required gene are selectively sensitive to an antibiotic acting via a particular pathway, then the gene against which the antisense acts is involved in the pathway in which the antibiotic acts.

G. Identification of Pathway in which a Test Antibiotic Acts

As discussed above, the cell based assay may also be used to determine the pathway against which a test antibiotic acts. In such an analysis, the pathways against which each member of a panel of antisense nucleic acids acts are identified as described above. A panel of cells, each containing an inducible antisense vector against a gene in a known proliferation-required pathway, is contacted with a test antibiotic for which it is desired to determine the pathway on which it acts under inducing an non-inducing conditions. If heightened sensitivity is observed in induced cells expressing antisense against a gene in a particular pathway but not in induced cells expressing

antisense against genes in other pathways, then the test antibiotic acts against the pathway for which heightened sensitivity was observed.

One skilled in the art will appreciate that further optimization of the assay conditions, such as the concentration of inducer used to induce antisense expression and/or the growth conditions used for the assay (for example incubation temperature and media components) may further increase the selectivity and/or magnitude of the antibiotic sensitization exhibited.

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The following example confirms the effectiveness of the methods described above.

EXAMPLE 11

Identification of the Pathway in which a Proliferation-Required Gene Lies

Antibiotics of various chemical classes and modes of action were purchased from Sigma Chemicals (St. Louis, MO). Stock solutions were prepared by dissolving each antibiotic in an appropriate aqueous solution based on information provided by the manufacturer. The final working solution of each antibiotic contained no more than 0.2% (w/v) of any organic solvent. To determine their potency against a bacterial strain engineered for expression of an antisense against a proliferation-required gene encoding 50S ribosomal protein, each antibiotic was serially diluted two or three fold in growth medium supplemented with the appropriate antibiotic for maintenance of the anti-sense construct. At least ten dilutions were prepared for each antibiotic. 25 µL aliquots of each dilution were transferred to discrete wells of a 384-well microplate (the assay plate) using a multichannel pipette. Quadruplicate wells were used for each dilution of an antibiotic under each treatment condition (plus and minus inducer). Each assay plate contained twenty wells for cell growth controls (growth media replacing antibiotic), ten wells for each treatment (plus and minus inducer, in this example IPTG). Assay plates were usually divided into the two treatments: half the plate containing induced cells and an appropriate concentrations of inducer (in this example IPTG) to maintain the state of induction, the other half containing non-induced cells in the absence of IPTG.

Cells for the assay were prepared as follows. Bacterial cells containing a construct, from which expression of antisense nucleic acid against rplL and rplJ, which encode proliferation-required 50S ribosomal subunit proteins, is inducible in the presence of IPTG, were grown into exponential growth (OD600 0.2 to 0.3) and then diluted 1:100 into fresh media containing either 400 μ M or 0 μ M inducer (IPTG). These cultures were incubated at 37° C for 2.5 hr. After a 2.5 hr incubation, induced and non-induced cells were respectively diluted into an assay medium at a final OD600 value of 0.0004. The medium contained an appropriate concentration of the antibiotic for the maintenance of the anti-sense construct. In addition, the medium used to dilute induced cells was supplemented with 800 μ M IPTG so that addition to the assay plate would result in a final IPTG concentration of 400 μ M. Induced and non-induced cell suspensions were dispensed (25 μ l/well) into the appropriate wells of the assay plate as discussed previously. The plate was then loaded into

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a plate reader, incubated at constant temperature, and cell growth was monitored in each well by the measurement of light scattering at 595 nm. Growth was monitored every 5 minutes until the cell culture attained a stationary growth phase. For each concentration of antibiotic, a percentage inhibition of growth was calculated at the time point corresponding to mid-exponential growth for the associated control wells (no antibiotic, plus or minus IPTG). For each antibiotic and condition (plus or minus IPTG), a plot of percent inhibition versus log of antibiotic concentration was generated and the IC50 determined. A comparison of the IC₅₀ for each antibiotic in the presence and absence of IPTG revealed whether induction of the antisense construct sensitized the cell to the mechanism of action exhibited by the antibiotic. Cells which exhibited a significant (standard statistical analysis) numerical decrease in the IC₅₀ value in the presence of inducer were considered to have an increased sensitivity to the test antibiotic.

The results are provided in the table below, which lists the classes and names of the antibiotics used in the analysis, the targets of the antibiotics, the IC50 in the absence of IPTG, the IC50 in the presence of IPTG, the concentration units for the IC50s, the fold increase in IC50 in the presence of IPTG, and whether increased sensitivity was observed in the presence of IPTG.

TABLE IV

Effect of Expression of Antisense RNA to rplL and rplJ on Antibiotic Sensitivity

ANTIBIOTIC CLASS /Names	TARGET	ICSO (-IPTG)	ICSO (+IPTG)	Conc.	ICS0 (-IPTG) ICS0 (+IPTG) Conc. Fold Increase Sensitivity	Sensitivity
				Unit	in Sensitivity Increased?	Increased?
PROTEIN SYNTHESIS INHIBITOR						
ANTIBIOTICS						
AMINOGLYCOSIDES						
Gentamicin	30S ribosome function	2715	19.19	ng/ml	141	Yes
Streptomycin	30S ribosome function	11280	161	ng/ml	02	Yes
Spectinomycin	30S ribosome function	18050	<156	ng/ml		Yes
Tobramycin	30S ribosome function	3594	70.58	ng/m1	51	Yes
MACROLIDES						
Erythromycin	50S ribosome function	7467	187	ng/ml	40	Yes
AROMATIC POYKETIDES			•			
Tetracycline	30S ribosome function	199.7	1.83	ng/ml	601	Yes
Minocycline	30S ribosome function	668.4	3.897	ng/ml	172	Yes
Doxycycline	30S ribosome function	413.1	27.81	ng/ml	15	Yes
OTHER PROTEIN SYNTHESIS INHIBITORS						
Fusidic acid	Elongation Factor G function	29990	641	ng/ml	8	Yes
Chloramphenicol	30S ribosome function	465.4	1.516	ng/mi	307	Yes
Lincomycin	50S ribosome function	47150	324.2	ng/ml	145	Yes

ANTIBIOTIC CLASS /Names	TARGET	ICSO (-IPTG)	(C50 (+IPTG)	Conc	ICS0 (-IPTG) ICS0 (+IPTG) Conc. Fold Increase Sensitivity	Sensitivity
				Unit	in Sensitivity Increased?	Increased?
OTHER ANTIBIOTIC MECHANISMS						
B-LACTAMS						
Cefoxitin	Cell wall biosynthesis	2782	2484	ng/ml	-	N _o
Cefotaxime	Cell wall biosynthesis	24.3	24.16	ng/ml	-	°Z
DNA SYNTHESIS INHIBITORS	•					
Nalidixic acid	DNA Gyrase activity	6973	6025	ng/ml	-	%
Ofloxacin	DNA Gyrase activity	49.61	45.89	ng/ml	-	ž
ОТНЕК						
Bacitracin	Cell membrane function	4077	4677	mg/ml	-	ž
Trimethoprim	Dihydrofolate Reductase activity	128.9	181.97	ng/ml	-	°Z
Vancomycin	Cell wall biosynthesis	145400	72550	lm/gu	2	No

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The above results demonstrate that induction of an antisense RNA to genes encoding 50S ribosomal subunit proteins results in a selective and highly significant sensitization of cells to antibiotics that inhibit ribosomal function and protein synthesis. The above results further demonstrate that induction of an antisense construct to an essential gene sensitizes an organism to compounds that interfere with that gene products' biological role. This sensitization is restricted to compounds that interfere with pathways associated with the targeted gene and it's product.

Assays utilizing antisense constructs to essential genes can be used to identify compounds that specifically interfere with the activity of multiple targets in a pathway. Such constructs can be used to simultaneously screen a sample against multiple targets in one pathway in one reaction (Combinatorial HTS).

Furthermore, as discussed above, panels of antisense construct containing cells may be used to characterize the point of intervention of any compound affecting an essential biological pathway including antibiotics with no known mechanism of action.

Another embodiment of the present invention is a method for determining the pathway against which a test antibiotic compound is active in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for determining which pathway a test antibiotic acts against except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required gene product is reduced using sublethal level of a known antibiotic which acts against the proliferation required gene product.

Interactions between drugs which affect the same biological pathway has been described in the literature. For example, Mecillinam (Amdinocillin) binds to and inactivates the penicillin binding protein 2 (PBP2, product of the *mrdA* in *E. coli*). This antibiotic inteacts with other antibiotics that inhibit PBP2 as well as antibiotics that inhibit other penicillin binding proteins such as PBP3 [(Gutmann, L., Vincent, S., Billot-Klein, D., Acar, J.F., Mrena, E., and Williamson, R. (1986) Involvement of penicillin-binding protein 2 with other penicillin-binding proteins in lysis of *Escherichia coli* by some beta-lactam antibiotics alone and in synergistic lytic effect of amdinocillin (mecillinam). Antimicrobial Agents & Chemotherapy, 30:906-912)]. Interactions between drugs could, therefore, involve two drugs that inhibit the same target protein or nucleic acid or inhibit different proteins or nucleic acids in the same pathway [(Fukuoka, T., Domon, H., Kakuta, M., Ishii, C., Hirasawa, A., Utsui, Y., Ohya, S., and Yasuda, H. (1997) Combination effect

between panipenem and vancomycin on highly methicillin-resistant Staphylococcus aureus. Japan. J. Antibio. 50:411-419; Smith, C.E., Foleno, B.E., Barrett, J.F., and Frosc, M.B. (1997) Assessment of the synergistic interactions of levofloxacin and ampicillin against Enterococcus faecium by the checkerboard agar dilution and time-kill methods. Diagnos. Microbiol. Infect. Disease 27:85-92; den Hollander, J.G., Horrevorts, A.M., van Goor, M.L., Verbrugh, H.A., and Mouton, J.W. (1997) Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. Antimicrobial Agents & Chemotherapy. 41:95-110)].

Two drugs may interact even though they inhibit different targets. For example, the proton pump inhibitor, Omeprazole, and the antibiotic, Amoxycillin, two synergistic compounds acting together, can cure *Helicobacter pylori* infection [(Gabryelewicz, A., Laszewicz, W., Dzieniszewski, J., Ciok, J., Marlicz, K., Bielecki, D., Popiela, T., Legutko, J., Knapik, Z., Poniewierka, E. (1997) Multicenter evaluation of dual-therapy (omeprazol and amoxycillin) for *Helicobacter pylori*-associated duodenal and gastric ulcer (two years of the observation). J. Physiol. Pharmacol. 48 Suppl 4:93-105)].

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The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

Cells are contacted with a combination of each member of a panel of known antibiotics at a sublethal level and varying concentrations of the test antibiotic. As a control, the cells are contacted with varying concentrations of the test antibiotic alone. The IC₅₀ of the test antibiotic in the presence and absence of the known antibiotic is determined. If the IC50s in the presence and absence of the known drug are substantially similar, then the test drug and the known drug act on different pathways. If the IC₅₀s are substantially different, then the test drug and the known drug act on the same pathway.

Another embodiment of the present invention is a method for identifying a candidate compound for use as an antibiotic in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for identifying candidate compounds for use as antibiotics except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required

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gene product is reduced using a sublethal level of a known antibiotic which acts against the proliferation required gene product.

The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

In order to characterize test compounds of interest, cells are contacted with a panel of known antibiotics at a sublethal level and one or more concentrations of the test compound. As a control, the cells are contacted with the same concentrations of the test compound alone. The IC₅₀ of the test compound in the presence and absence of the known antibiotic is determined. If the IC₅₀ of the test compound is substantially different in the presence and absence of the known drug then the test compound is a good candidate for use as an antibiotic. As discussed above, once a candidate compound is identified using the above methods its structure may be optimized using standard techniques such as combinatorial chemistry.

Representative known antibiotics which may be used in each of the above methods are provided in the table below. However, it will be appreciated that other antibiotics may also be used.

ANTIBIOTIC	INHIBITS/TARGET	RESISTANT
		MUTANTS
Inhibitors of Transcription		
Rifamycin, 1959 Rifampicin Rifabutin Rifaximin	Inhibits initiation of transcription/\(\beta\)-subunit RNA polymerase, \(rpoB\)	rpoB, crp, cyaA
Streptolydigin	Accelerates transcription chain termination/B-subunit RNA polymerase	rpoB
Streptovaricin	an acyclic ansamycin, inhibits RNA polymerase	гроВ
Actinomycin D+EDTA	Intercalates between 2 successive G-C pairs, <i>rpoB</i> , inhibits RNA synthesis	pldA
Inhibitors of Nucleic Acid Met	tabolism	
Quinolones, 1962 Nalidixic	α subunit gyrase and/or topoisomerase IV,	
acid Oxolinic acid	gyrA	gyrAorB, icd, sloB
Fluoroquinolones	α subunit gyrase, gyrA and/or	gyrA
Ciprofloxacin, 1983 Norfloxacin	topoisomerase IV (probable target in Staph)	norA (efflux in Staph) hipQ
Coumerins Novobiocin	Inhibits ATPase activity of B-subunit	
	gyrase, gyrB	gyrB, cysB, cysE, nov, ompA
Coumermycin	Inhibits ATPase activity of B-subunit gyrase, gyrB	gyrB, hisW
Albicidin	DNA synthesis	tsx (nucleoside channel)
Metronidazole	Causes single-strand breaks in DNA	nar

Inhibitana of Metabalia Dathua	T. P.	
Inhibitors of Metabolic Pathwa Sulfonamides, 1932	blocks synthesis of dihydrofolate, dihydro-	folP, gpt, pabA, pabB,
Sulfanilamide	pteroate synthesis, folP	pabC
Trimethoprim, 1962	Inhibits dihydrofolate reductase, folA	folA, thyA
Showdomycin	Nucleoside analogue capable of alkylating	nupC, pnp
• · · · · · · · · · · · · · · · · · · ·	sulfhydryl groups, inhibitor of thymidylate	• • •
	synthetase	
Thiolactomycin	type II fatty acid synthase inhibitor	emrB
		fadB, emrB due to gene
		dosage
Psicofuranine	Adenosine glycoside antibiotic, target is	guaA,B
	GMP synthetase	
Triclosan	Inhibits fatty acid synthesis	fabl (envM)
Diazoborines Isoniazid,	heterocyclic, contains boron, inhibit fatty	fabl (envM)
Ethionamide	acid synthesis, enoyl-ACP reductase, fabl	
Inhibitors of Translation		
Phenylpropanoids	Binds to ribosomal peptidyl transfer center	•
Chloramphenicol, 1947	preventing peptide translocation/ binds to	rrn, cmlA, marA, ompF,
· Omoramphomoot, 15 tr	S6, L3, L6, L14, L16, L25, L26, L27, but	ompR
	preferentially to L16	
Tetracyclines, 1948, type II	Binding to 30S ribosomal subunit, "A" site	clmA (cmr), mar, ompF
polyketides	on 30S subunit, blocks peptide elongation,	(s), , , , , , ,
Minocycline	strongest binding to S7	
Doxycycline	5	
Macrolides (type I polyketides)	Binding to 50 S ribosomal subunit, 23S	
Erythromycin, 1950	rRNA, blocks peptide translocation, L15,	
Carbomycin, Spiramycin	L4, L12	rrn, rplC, rplD, rplV,
	•	mac
etc		
Aminoglycosides Streptomycin,	Irreversible binding to 30S ribosomal	1 . 6 1/ 1/5
1944	subunit, prevents translation or causes	rpsL, strC,M, ubiF
Neomycin	mistranslation of mRNA/16S rRNA	atpA-E, ecfB,
		hemAC,D,E,G, topA,
Spectinomycin	•	rpsC,D,E, rrn, spcB atpA-atpE, cpxA, ecfB,
·		
		ham A R I ton A
Kanamycin		hemA,B,L, topA
Kanamycin		hemA,B,L, topA ksgA,B,C,D, rplB,K,
Kanamycin Kasugamycin		hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R
Kasugamycin		hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF
Kasugamycin Gentamicin, 1963		hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA
Kasugamycin Gentamicin, 1963 Amikacin		hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF
Kasugamycin Gentamicin, 1963 Amikacin Paromycin		hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides	Binding to 50 S ribosomal subunit, blocks	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955	Binding to 50 S ribosomal subunit, blocks peptide translocation	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin	peptide translocation	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin,	peptide translocation 2 components, Streptogramins A&B, bind	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation	hemA,B,L, topA ksgA,B,C,D, rplB,K,
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G)	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes Fusidic Acid	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G) prevents peptide translocation	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL linB, rplN,O, rpsG
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G) prevents peptide translocation Inhibition of elongation factor TU (EF-Tu),	hemA,B,L, topA ksgA,B,C,D, rplB,K,
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes Fusidic Acid Kirromycin (Mocimycin)	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G) prevents peptide translocation Inhibition of elongation factor TU (EF-Tu), prevents peptide bond formation	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL linB, rplN,O, rpsG
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes Fusidic Acid Kirromycin (Mocimycin) Pulvomycin	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G) prevents peptide translocation Inhibition of elongation factor TU (EF-Tu), prevents peptide bond formation Binds to and inhibits EF-TU	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL linB, rplN,O, rpsG fusA tufA,B
Kasugamycin Gentamicin, 1963 Amikacin Paromycin Lincosamides Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin Fusidanes Fusidic Acid Kirromycin (Mocimycin)	peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation Inhibition of elongation factor G (EF-G) prevents peptide translocation Inhibition of elongation factor TU (EF-Tu), prevents peptide bond formation	hemA,B,L, topA ksgA,B,C,D, rplB,K, rpsI,N,M,R rplF, ubiF cpxA rpsL linB, rplN,O, rpsG

Tiamulin Inhibits protein synthesis rplC, rplD Negamycin Inhibits termination process of protein prfB synthesis

Oxazolidinones Linezolid 23S rRNA

Isoniazid

pdx Nitrofurantoin Inhibits protein synthesis, nitroreductases nfnA,B convert nitrofurantoin to highly reactive

> electrophilic intermediates which attack bacterial ribosomal proteins non-

specifically

Pseudomonic Acids Mupirocin

(Bactroban)

Inhibition of isoleucyl tRNA synthetaseused for Staph, topical cream, nasal

Indolmycin Viomycin

Inhibits tryptophanyl-tRNA synthetase

rrmA (23S rRNA methyltransferase; mutant has slow growth rate, slow chain elongation rate,

and viomycin resistance)

envZ, galU, hipA,

ileS

trpS

Thiopeptides Binds to L11-23S RNA complex Thiostrepton

Inhibits GTP hydrolysis by EF-G Stimulates GTP hydrolysis by EF-G

Inhibitors of Cell Walls/Membranes

Micrococcin

B-lactams Inhibition of one or more cell wall Penicillin, 1929 Ampicillin transpeptidases, endopeptidases, and

glycosidases (PBPs), of the 12 PBPs only 2 ampC, ampD, ampE, Methicillin, 1960

are essential: mrdA (PBP2) and ftsI (pbpB, PBP3)

hipQ, ompC, ompF, ompR, ptsI, rfa,

tolD, tolE

Cephalosporins, 1962 tonB

Binds to and inactivates PBP2 (mrdA) alaS, argS, crp, cyaA, Mecillinam (amdinocillin) Inactivates PBP3 (fts/) envB, mrdA,B,

mreB,C,D Aztreonam (Furazlocillin) dppA

Bacilysin, Tetaine Dipeptide, inhib glucosamine synthase Glycopeptides Vancomycin, 1955 Inhib G+ cell wall syn, binds to terminal

D-ala-D-ala of pentapeptide, Polypeptides Prevents dephosphorylation and Bacitracin

regeneration of lipid carrier rfa

Cyclic lipopeptide Daptomycin, Disrupts multiple aspects of membrane 1980 function, including peptidoglycan

synthesis, lipoteichoic acid synthesis, and the bacterial membrane potential

Cyclic polypeptides Polymixin, Surfactant action disrupts cell membrane pmrA

1939 lipids, binds lipid A mioety of LPS Fosfomycin, 1969 Analogue of P-enolpyruvate, inhibits 1st murA, crp, cyaA glpT, step in peptidoglycan synthesis - UDP-NhipA, ptsI, uhpT

acetylglucosamine enolpyruvyl transferase, murA. Also acts as Immunosuppressant

Cycloserine Prevents formation of D-ala dimer, hipA, cycA inhibits D-ala ligase, ddlA,B

Alafosfalin phosphonodipeptide, cell wall synthesis pepA, tpp

inhibitor, potentiator of β-lactams

Inhibitors of Protein Processing/Transport

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Globomycin Inhibits signal peptidase II (cleaves

prolipoproteins subsequent to lipid modification, *lspA*

lpp, dnaE

EXAMPLE 12

Transfer of Exogenous Nucleic Acid Sequences to other Bacterial Species Using the E. coli Expression Vectors or Expression Vectors Functional in Bacterial Species other than E. coli.

Molecule No. EcXA059, encoding a portion of the ypjA gene of Escherichia coli, was either transformed directly into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae or subcloned into an expression vector functional in these species and the subclones transformed into these organisms. Suitable expression vectors are well known in the art. These expression vectors were introduced into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae cells that were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. If there was no effect of antisense RNA expression in one organism, the clone is given a score of zero "0" in that organism. In contrast, a score of "8" means that 10⁸ times more cells were required to observe a colony formed on the induced state than in the non-induced state under the conditions used and in that organism.

Expression vectors containing Molecule No. EcXA059 were found to inhibit bacterial growth in all four organisms when expression of the antisense RNA was induced with IPTG. A score of 8 was assigned for *Escherichia coli*, *Enterobacter cloacae*, and *Salmonella typhimurium* and in *Klebsiella pneumoniae* the score was >7. The protein encoded by this sequence is used as a target sequence to screen candidate compound libraries as described above.

In addition, the above methods were validated using other antisense nucleic acids which inhibit the growth of *E. coli* which were identified using methods similar to those described above. Expression vectors which inhibited growth of *E. coli* upon induction of antisense RNA expression with IPTG were transformed directly into *Enterobacter cloacae*, *Klebsiella pneumonia* or *Salmonella typhimurium*. The transformed cells were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. The results of these experiments are listed in Table V below. If there was no effect of antisense RNA expression in a microorganism, the clone is minus in Table V below. In

contrast, a positive in Table V below means that at least 10 fold more cells were required to observe a colony on the induced plate than on the non-induced plate under the conditions used and in that microorganism.

Sixteen of the constructs were found to inhibit growth in all the microorganisms tested upon induction of antisense RNA expression with IPTG.

TABLE V

Sensitivity of Other Microorganisms to Antisense Nucleic Acids That Inhibit Proliferation in E. coli

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA001	+	+	-
EcXA004	+	-	-
EcXA005	+	+	+
EcXA006	•	-	-
EcXA007	•	+	-
EcXA008	+	•	+
EcXA009	•	-	-
EcXA010	+	+	+
EcXA011	-	+	•
EcXA012	-	+	-
EcXA013	+	+	+
EcXA014	+	+	•
EcXA015	+	+	+
EcXA016	+	+	+
EcXA017	+	+	+
EcXA018	+	+	+
EcXA019	+	+	+
EcXA020	+	+	+
EcXA021	+	+	+
EcXA023	+	+	+
EcXA024	+	-	+
EcXA025	•	•	•
EcXA026	+	+	-
EcXA027	+	+	-
EcXA028	+	-	-
EcXA029	-	-	-
EcXA030	+	+	+
EcXA031	+	-	-
EcXA032	+	+	-
EcXA033	+	+	+
EcXA034	+	+	+
EcXA035	-		-
EcXA036	+	-	+
EcXA037	+	+	-
EcXA038	+	+	+
EcXA039	+	•	-
EcXA041	+	+	+
EcXA042	-	+	+

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Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA043	<u>-</u>	<u>-</u>	
EcXA044	•	•	•
EcXA045	+	+	+
EcXA046	•	-	-
EcXA047	+	+	-
EcXA048	•	•	-
EcXA049	+	-	-
EcXA050	.		-
EcXA051	+	-	-
EcXA052	+	• *	-
EcXA053	+	+	+
EcXA054	•	•	+
EcXA055	+	-	•
EcXA056	+	-	+
EcXA057	+	+	-
EcXA058		-	-
EcXA059	+	+	+
EcXA060	<u>.</u>	•	-
EcXA061	-	-	•
EcXA062	-	.•	-
EcXA063	+	+	
EcXA064	•	-	-
EcXA065	+	+	
EcXA066	•	•	-
EcXA067		+	-
EcXA068	-	-	
EcXA069	-	+	-
EcXA070	•	•	•
EcXA071	+	-	-
EcXA072	+		+
EcXA073	+	+	+
EcXA074	+	+	+
EcXA075	+	•	-
EcXA076	-	+	-
EcXA077	+	+	-
EcXA079	+	+	+
EcXA080	+	•	-
EcXA082	-	+	• .
EcXA083	-	-	-
EcXA084	•	+	•
EcXA086	-	•	-
EcXA087	-		-
EcXA088	-		
EcXA089	-	=	_
EcXA090	-	-	•
EcXA091	-	<u> </u>	
EcXA092	•	-	_
EcXA093	-	-	_
20/010/5			L

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA094	+	+	+
EcXA095	+	+	-
EcXA096	-	-	-
EcXA097	+	-	•
EcXA098	+	-	*
EcXA099	-	•	-
EcXA100	•	-	•
EcXA101	-	-	•
EcXA102	-	-	•
EcXA103	-	+	-
EcXA104	+	+	+
EcXA106	+	+	-
EcXA107	-	-	-
EcXA108	-	-	-
EcXA109	-	-	-
EcXA110	+	+	-
EcXA111	_	_	•
EcXA112		+	•
EcXA113	+	+	+
EcXA114		+	
EcXA115		+	
EcXA116	+	+	
EcXA117	+	-	•
EcXA118	-	<u>-</u>	•
EcXA119	+	+	•
EcXA120	•	-	
EcXA121			•
EcXA122	+	-	+
EcXA123	+	_	-
EcXA124	_	_	
EcXA125	1 .	_	•
EcXA126	-	-	-
EcXA127	+	+	····
EcXA127	 	<u> </u>	
EcXA128	-	+	-
EcXA130	+	+	
EcXA130	-		
EcXA132 EcXA133	1	- -	<u> </u>
	-	-	-
EcXA136		-	
EcXA137		-	-
EcXA138	+		•
EcXA139		-	
EcXA140	+	-	•
EcXA141	+	•	-
EcXA142	-	-	•
EcXA143	•	+	
EcXA144	+	+	<u> </u>
EcXA145	•	•	-

Mol No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA146	-	-	-
EcXA147	-	-	-
EcXA148	-	•	-
EcXA149	+	+	+
EcXA150	-	-	-
EcXA151	+	-	-
EcXA152	-	· ·	-
EcXA153	+	+	-
EcXA154	-	•	-
EcXA155	-	-	ND
EcXA156	-	+	-
EcXA157	_	-	-
EcXA158	-	-	-
EcXA159	+	-	-
EcXA160	+	-	
EcXA162		-	
EcXA163	•	-	-
EcXA164	-		-
EcXA165	-	-	
EcXA166	•	-	-
EcXA167	•	-	-
EcXA168	-	•	-
EcXA169	-	+	
EcXA171		-	-
EcXA172	† 	-	_
EcXA173	-	•	•
EcXA174		-	
EcXA175	-	-	-
EcXA176	-		•
EcXA178	•		-
EcXA179	-	-	-
EcXA180	+	-	-
EcXA181	_	-	+
EcXA182	-	•	•
EcXA183	-	•	-
EcXA184	-		-
EcXA185	<u> </u>	-	-
EcXA186	-	-	
EcXA187	+	+	+
EcXA189	+	-	-
EcXA190	+	+	+
EcXA190	+	+	- :
EcXA191 EcXA192	 	+	-
ECAA192		т	<u> </u>

Thus, the ability of an antisense nucleic acid which inhibits the proliferation of *E. coli* to inhibit the growth of other organims may be evaluated by either transforming the antisense nucleic acid directly into other *Escherichia* species or inserting the antisense nucleic acid into expression

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vectors that are functional in other Gram negative species such as Enterobacter cloacae, Salmonella typhimurium, and/or Klebsiella pneumoniae. Similarly, the antisense nucleic acid can be inserted in expression vectors that are functional in Gram-positive species such as Staphylococcus aureus, Enterococcus faecalis and Streptococcus pneumoniae or other species.

Those skilled in the art will appreciate that a negative result in a heterologous microorganism does not mean that that microorganism is missing that gene nor does it mean that the gene is unessential. However, a positive result means that the heterologous microorganism contains a homologous gene which is required for proliferation of that microorganism. The homologous gene may be obtained using the methods described herein. Those cells that are inhibited by antisense may be used in cell based assays as described herein for the identification and characterization of compounds in order to develop antibiotics effective in these microorganisms. Those skilled in the art will appreciate that an antisense molecule which works in the microorganism from which it was obtained will not always work in a heterologous microorganism.

EXAMPLE 13

Use of Identified Exogenous Nucleic Acid Sequences as Probes

The identified sequence of the present invention can be used as probes to obtain the sequence of additional genes of interest from a second organism. For example, probes to potential bacterial target proteins may be hybridized to nucleic acids from other organisms including other bacteria and higher organisms, to identify homologous sequences. Such hybridization might indicate that the protein encoded by the gene to which the probe corresponds is found in humans and therefore not necessarily a good drug target. Alternatively, the gene can be conserved only in bacteria and therefore would be a good drug target for a broad spectrum antibiotic or antimicrobial.

Probes derived from the identified nucleic acid sequences of interest or portions thereof can be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe can be single stranded or double stranded and can be made using techniques known in the art, including *in vitro* transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it can be denatured prior to contacting the probe. In some applications, the nucleic acid sample can be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample can comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe can be cloned into vectors such as expression vectors, sequencing vectors, or in

vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques can be used to isolate, purify and clone sequences from a genomic library, made from a variety of bacterial species, which are capable of hybridizing to probes made from the sequences identified in Examples 5 and 6.

EXAMPLE 14

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Preparation of PCR Primers and Amplification of DNA

The identified E. coli genes corresponding directly to or located within the operon of nucleic acid sequences required for proliferation or portions thereof can be used to prepare PCR primers for a variety of applications, including the identification or isolation of homologous sequences from other species, for example S. typhimurium, E. cloacae, and Klebsiella pneumoniae, which contain part or all of the homologous genes. Because homologous genes are related but not identical in sequence, those skilled in the art will often employ degenerate sequence PCR primers. Such degenerate sequence primers are designed based on conserved sequence regions, either known or suspected, such as conserved coding regions. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. The PCR primers are at least 10 bases, and preferably at least 20 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers can be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. When the entire coding sequence of the target gene is known, the 5' and 3' regions of the target gene can be used as the sequence source for PCR probe generation. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

EXAMPLE 15

Inverse PCR

The technique of inverse polymerase chain reaction can be used to extend the known nucleic acid sequence identified in Examples 5 and 6. The inverse PCR reaction is described generally by Ochman et al., in Ch. 10 of PCR Technology: Principles and Applications for DNA Amplification, (Henry A. Erlich, Ed.) W.H. Freeman and Co. (1992). Traditional PCR requires two primers that are

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used to prime the synthesis of complementary strands of DNA. In inverse PCR, only a core sequence need he known.

Using the sequences identified as relevant from the techniques taught in Examples 5 and 6 and applied to other species of bacteria, a subset of exogenous nucleic sequences are identified that correspond to genes or operons that are required for bacterial proliferation. In species for which a genome sequence is not known, the technique of inverse PCR provides a method for obtaining the gene in order to determine the sequence or to place the probe sequences in full context to the target sequence to which the identified exogenous nucleic acid sequence binds.

To practice this technique, the genome of the target organism is digested with an appropriate restriction enzyme so as to create fragments of nucleic acid that contain the identified sequence as well as unknown sequences that flank the identified sequence. These fragments are then circularized and become the template for the PCR reaction. PCR primers are designed in accordance with the teachings of Example 15 and directed to the ends of the identified sequence are synthesized. The primers direct nucleic acid synthesis away from the known sequence and toward the unknown sequence contained within the circularized template. After the PCR reaction is complete, the resulting PCR products can be sequenced so as to extend the sequence of the identified gene past the core sequence of the identified exogenous nucleic acid sequence identified. In this manner, the full sequence of each novel gene can be identified. Additionally the sequences of adjacent coding and noncoding regions can be identified.

EXAMPLE 16

Identification of Genes Required for Staphylococcus aureus Proliferation

Genes required for proliferation in *Staphylococcus aureus* are identified according to the methods described above.

EXAMPLE 17

Identification of Genes Required for Neisseria gonorrhoeae Proliferation

Genes required for proliferation in *Neisseria gonorrhoeae* are identified according to the methods described above.

EXAMPLE 18

Identification of Genes Required for Pseudomonas aeruginosa Proliferation

Genes required for proliferation in *Pseudomonas aeruginosa* are identified according to the methods described above.

EXAMPLE 19

Identification of Genes Required for Enterococcus faecalis Proliferation

Genes required for proliferation in *Enterococcus faecalis* are identified according to the methods described above.

EXAMPLE 20

Identification of Genes Required for Haemophilus influenzae Proliferation

Genes required for proliferation in *Haemophilus influenzae* are identified according to the methods described above.

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EXAMPLE 21

Identification of Genes Required for Salmonella typhimurium Proliferation

Genes required for proliferation in Salmonella typhimurium are identified according to the methods described above.

EXAMPLE 22

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Identification of Genes Required for Helicobacter pylori Proliferation

Genes required for proliferation in *Helicobacter pylori* are identified according to the methods described above.

EXAMPLE 23

Identification of Genes Required for Mycoplasma pneumoniae Proliferation

Genes required for proliferation in *Mycoplasma pneumoniae* are identified according to the methods described above.

EXAMPLE 24

Identification of Genes Required for Plasmodium ovale Proliferation

Genes required for proliferation in *Plasmodium ovale* are identified according to the methods described above.

EXAMPLE 25

Identification of Genes Required for Saccharomyces cerevisiae Proliferation

Genes required for proliferation in Saccharomyces cerevisiae are identified according to the methods described above.

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EXAMPLE 26

Identification of Genes Required for Entamoeba histolytica Proliferation

Genes required for proliferation in *Entamoeba histolytica* are identified according to the methods described above.

EXAMPLE 27

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Identification of Genes Required for Candida albicans Proliferation

Genes required for proliferation in *Candida albicans* are identified according to the methods described above.

EXAMPLE 28

Identification of Genes Required for Klebsiella pneumoniae Proliferation

Genes required for proliferation in *Klebsiella pneumoniae* are identified according to the methods described above.

5 EXAMPLE 29

Identification of Genes Required for Salmonella typhi Proliferation

Genes required for proliferation in Salmonella typhi are identified according to the methods described above.

EXAMPLE 30

10 Identification of Genes Required for Salmonella paratyphi Proliferation

Genes required for proliferation in Salmonella paratyphi are identified according to the methods described above.

EXAMPLE 31

Identification of Genes Required for Salmonella cholerasuis Proliferation

Genes required for proliferation in Salmonella cholerasuis are identified according to the methods described above.

EXAMPLE 32

Identification of Genes Required for Staphylococcus epidermis Proliferation

Genes required for proliferation in *Staphylococcus epidermis* are identified according to the methods described above.

EXAMPLE 33

Identification of Genes Required for Mycobacterium tuberculosis Proliferation

Genes required for proliferation in *Mycobacterium tuberculosis* are identified according to the methods described above.

25 EXAMPLE 34

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Identification of Genes Required for Mycobacterium leprae Proliferation

Genes required for proliferation in *Mycobacterium leprae* are identified according to the methods described above.

EXAMPLE 35

30 <u>Identification of Genes Required for Treponema pallidum Proliferation</u>

Genes required for proliferation in *Treponema pallidum* are identified according to the methods described above.

EXAMPLE 36

Identification of Genes Required for Bacillus anthracis Proliferation

35 Genes required for proliferation in *Bacillus anthracis* are identified according to the methods described above.

EXAMPLE 37

Identification of Genes Required for Yersinia pestis Proliferation

Genes required for proliferation in Yersinia pestis are identified according to the methods described above.

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EXAMPLE 38

Identification of Genes Required for Clostridium botulinum Proliferation

Genes required for proliferation in *Clostridium botulinum* are identified according to the methods described above.

EXAMPLE 39

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Identification of Genes Required for Campylobacter jejuni Proliferation

Genes required for proliferation in *Campylobacter jejuni* are identified according to the methods described above.

EXAMPLE 40

Identification of Genes Required for Chlamydia trachomatis Proliferation

Genes required for proliferation in *Chlamydia trachomatis* are identified according to the methods described above.

Use of Isolated Exogenous Nucleic Acid Fragments as Antisense Antibiotics

In addition to using the identified sequences to enable screening of molecule libraries to identify compounds useful to identify antibiotics, the sequences themselves can be used as therapeutic agents. Specifically, the identified exogenous sequences in an antisense orientation can be provided to an individual to inhibit the translation of a bacterial target gene.

Generation of Antisense Therapeutics from Identified Exogenous Sequences

The sequences of the present invention can be used as antisense therapeutics for the treatment of bacterial infections or simply for inhibition of bacterial growth in vitro or in vivo. The therapy exploits the biological process in cells where genes are transcribed into messenger RNA (mRNA) that is then translated into proteins. Antisense RNA technology contemplates the use of antisense oligonucleotides directed against a target gene that will bind to its target and decrease or inhibit the translation of the target mRNA. In one embodiment, antisense oligonucleotides can be used to treat and control a bacterial infection of a cell culture containing a population of desired cells contaminated with bacteria. In another embodiment, the antisense oligonucleotides can be used to treat an organism with a bacterial infection.

Antisense oligonucleotides can be synthesized from any of the sequences of the present invention using methods well known in the art. In a preferred embodiment, antisense oligonucleotides are synthesized using artificial means. Uhlmann & Peymann, Chemical Rev. 90:543-584 (1990) review antisense oligonucleotide technology in detail. Modified or unmodified

antisense oligonucleotides can be used as therapeutic agents. Modified antisense oligonucleotides are preferred since it is well known that antisense oligonucleotides are extremely unstable. Modification of the phosphate backbones of the antisense oligonucleotides can be achieved by substituting the internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate bridges, thioester bridges, as well as many others known in the art. The preparation of certain antisense oligonucleotides with modified internucleotide linkages is described in U.S. Patent No. 5,142,047.

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Modifications to the nucleoside units of the antisense oligonucleotides are also contemplated. These modifications can increase the half-life and increase cellular rates of uptake for the oligonucleotides in vivo. For example, α -anomeric nucleotide units and modified bases such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-l-phenylribofuranose, and N^4 , N^4 -ethano-5-methyl-cytosine are contemplated for use in the present invention.

An additional form of modified antisense molecules is found in peptide nucleic acids. Peptide nucleic acids (PNA) have been developed to hybridize to single and double stranded nucleic acids. PNA are nucleic acid analogs in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units. Unlike DNA, which is highly negatively charged, the PNA backbone is neutral. Therefore, there is much less repulsive energy between complementary strands in a PNA-DNA hybrid than in the comparable DNA-DNA hybrid, and consequently they are much more stable. PNA can hybridize to DNA in either a Watson/Crick or Hoogsteen fashion (Demidov et al., *Proc. Natl. Acad. Sci. U.S.A.* 92:2637-2641, 1995; Egholm, *Nature* 365:566-568, 1993; Nielsen et al., *Science* 254:1497-1500, 1991; Dueholm et al., *New J. Chem.* 21:19-31, 1997).

Molecules called PNA "clamps" have been synthesized which have two identical PNA sequences joined by a flexible hairpin linker containing three 8-amino-3,6-dioxaoctanoic acid units. When a PNA clamp is mixed with a complementary homopurine or homopyrimidine DNA target sequence, a PNA-DNA-PNA triplex hybrid can form which has been shown to be extremely stable (Bentin et al., *Biochemistry* 35:8863-8869, 1996; Egholm et al., *Nucleic Acids Res.* 23:217-222, 1995; Griffith et al., *J. Am. Chem. Soc.* 117:831-832, 1995).

The sequence-specific and high affinity duplex and triplex binding of PNA have been extensively described (Nielsen et al., Science 254:1497-1500, 1991; Egholm et al., J. Am. Chem. Soc. 114:9677-9678, 1992; Egholm et al., Nature 365:566-568, 1993; Almarsson et al., Proc. Natl. Acad. Sci. U.S.A. 90:9542-9546, 1993; Demidov et al., Proc. Natl. Acad. Sci. U.S.A. 92:2637-2641, 1995). They have also been shown to be resistant to nuclease and protease digestion (Demidov et al., Biochem. Pharm. 48:1010-1313, 1994). PNA has been used to inhibit gene expression (Hanvey et al., Science 258:1481-1485,1992; Nielsen et al., Nucl. Acids. Res., 21:197-200, 1993; Nielsen et al., Gene

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149:139-145, 1994; Good & Nielsen, Science, 95: 2073-2076, 1998), to block restriction enzyme activity (Nielsen et al., supra, 1993), to act as an artificial transcription promoter (Mollegaard, Proc. Natl. Acad. Sci. U.S.A. 91:3892-3895, 1994) and as a pseudo restriction endonuclease (Demidov et al., Nucl. Acids. Res. 21:2103-2107, 1993). Recently, PNA has also been shown to have antiviral and antitumoral activity mediated through an antisense mechanism (Norton, Nature Biotechnol., 14:615-619, 1996; Hirschman et al., J. Investig. Med. 44:347-351, 1996). PNAs have been linked to various peptides in order to promote PNA entry into cells (Basu et al., Bioconj. Chem. 8:481-488, 1997; Pardridge et al., Proc. Natl. Acad. Sci. U.S.A. 92:5592-5596, 1995).

The antisense oligonucleotides contemplated by the present invention can be administered by direct application of oligonucleotides to a target using standard techniques well known in the art. The antisense oligonucleotides can be generated within the target using a plasmid, or a phage. Alternatively, the antisense nucleic acid may be expressed from a sequence in the chromosome of the target cell. It is further contemplated that contemplated that the antisense oligonucleotide contemplated are incorporated in a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991). The present invention also contemplates using a retron to introduce an antisense oligonucleotide to a cell. Retron technology is exemplified by U.S. Patent No. 5,405,775. Antisense oligonucleotides can also be delivered using liposomes or by electroporation techniques which are well known in the art.

The antisense nucleic acids of the present invention can also be used to design antibiotic compounds comprising nucleic acids which function by intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. The sequences identified as required for proliferation in the present invention, or portions thereof, can be used as templates to inhibit microorganism gene expression in individuals infected with such organisms. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences based on the sequences of the present invention that are required for proliferation are contemplated for use as antibiotic compound templates.

The antisense oligonucleotides of this example employ the identified sequences of the present invention to induce bacterial cell death or at least bacterial stasis by inhibiting target gene translation. Antisense oligonucleotides containing from about 8 to 40 bases of the sequences of the present invention have sufficient complementary to form a duplex with the target sequence under physiological conditions.

To kill bacterial cells or inhibit their growth, the antisense oligonucleotides are applied to the bacteria or to the target cells under conditions that facilitate their uptake. These conditions

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include sufficient incubation times of cells and oligonucleotides so that the antisense oligonucleotides are taken up by the cells. In one embodiment, an incubation period of 7-10 days is sufficient to kill bacteria in a sample. An optimum concentration of antisense oligonucleotides is selected for use.

The concentration of antisense oligonucleotides to be used can vary depending on the type of bacteria sought to be controlled, the nature of the antisense oligonucleotide to be used, and the relative toxicity of the antisense oligonucleotide to the desired cells in the treated culture. Antisense oligonucleotides can be introduced to cell samples at a number of different concentrations preferably between $1 \times 10^{-10} M$ to $1 \times 10^{-4} M$. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of 1×10^{-7} translates into a dose of approximately 0.6 mg/kg body weight. Levels of oligonucleotide approaching 100 mg/kg body weight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the subject are removed, treated with the antisense oligonucleotide, and reintroduced into the subject. This range is merely illustrative and one of skill in the art are able to determine the optimal concentration to be used in a given case.

After the bacterial cells have been killed or controlled in a desired culture, the desired cell population may be used for other purposes.

EXAMPLE 41

The following example demonstrates the ability of an *E. coli* antisense oligonucleotide to act as a bactericidal or bacteriostatic agent to treat a contaminated cell culture system. The application of the antisense oligonucleotides of the present invention are thought to inhibit the translation of bacterial gene products required for proliferation.

The antisense oligonucleotide of this example corresponds to a 30 base phophorothioate modified oligodeoxynucelotide complementary to a nucleic acid involved in proliferation, such as Molecule Number EcXA056 (SEQ ID NO: 1). A sense oligodeoxynucelotide complementary to the antisense sequence is synthesized and used as a control. The oligonucleotides are synthesized and purified according to the procedures of Matsukura, et al., Gene 72:343 (1988). The test oligonucleotides are dissolved in a small volume of autoclaved water and added to culture medium to make a 100 micromolar stock solution.

Human bone marrow cells are obtained from the peripheral blood of two patients and cultured according standard procedures well known in the art. The culture is contaminated with the K-12 strain of *E. coli* and incubated at 37°C overnight to establish bacterial infection.

The control and antisense oligonucleotide containing solutions are added to the contaminated cultures and monitored for bacterial growth. After a 10 hour incubation of culture and oligonucleotides, samples from the control and experimental cultures are drawn and analyzed

for the translation of the target bacterial gene using standard microbiological techniques well known in the art. The target *E. coli* gene is found to be translated in the control culture treated with the control oligonucleotide, however, translation of the target gene in the experimental culture treated with the antisense oligonucleotide of the present invention is not detected or reduced.

EXAMPLE 42

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A subject suffering from an *E. coli* infection is treated with the antisense oligonucleotide preparation of Example 39. The antisense oligonucleotide is provided in a pharmaceutically acceptable carrier at a concentration effective to inhibit the translation of the target gene. The present subject is treated with a concentration of antisense oligonucleotide sufficient to achieve a blood concentration of about 100 micromolar. The patient receives daily injections of antisense oligonucleotide to maintain this concentration for a period of 1 week. At the end of the week a blood sample is drawn and analyzed for the presence or absence using standard techniques well known in the art. There is no detectable evidence of E. coli and the treatment is terminated.

EXAMPLE 43

Preparation and use of Triple Helix Probes

The sequences of microorganism genes required for proliferation of the present invention are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches that could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into a population of bacterial cells that normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides can be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for a reduction in proliferation using techniques such as monitoring growth levels as compared to untreated cells using optical density measurements. The oligonucleotides that are effective in inhibiting gene expression in cultured cells can then be introduced in vivo using the techniques well known in that art at a dosage level shown to be effective.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-971 (1989)).

EXAMPLE 44

Identification of Bacterial Strains from Isolated Specimens by PCR

Classical bacteriological methods for the detection of various bacterial species are time consuming and costly. These methods include growing the bacteria isolated from a subject in specialized media, cultivation on selective agar media, followed by a set of confirmation assays that can take from 8 to 10 days or longer to complete. Use of the identified sequences of the present invention provides a method to dramatically reduce the time necessary to detect and identify specific bacterial species present in a sample.

In one exemplary method, bacteria are grown in enriched media and DNA samples are isolated from specimens of, for example, blood, urine, stool, saliva or central nervous system fluid by conventional methods. A panel of PCR primers based on identified sequences unique to various species of microorganisms are then utilized in accordance with Example 12 to amplify DNA of approximately 100-200 bases in length from the specimen. A separate PCR reaction is set up for each pair of PCR primers and after the PCR reaction is complete, the reaction mixtures are assayed for the presence of PCR product. The presence or absence of bacteria from the species to which the PCR primer pairs belong is determined by the presence or absence of a PCR product in the various test PCR reaction tubes.

Although the PCR reaction is used to assay the isolated sample for the presence of various bacterial species, other assays such as the Southern blot hybridization are also contemplated.

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WHAT IS CLAIMED IS:

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1. A purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 1-127, wherein expression of said nucleic acid inhibits proliferation of a microorganism.

- 2. The nucleic acid sequence of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a microorganism.
 - 3. The nucleic acid of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of an RNA required for proliferation of a microorganism.
- 4. The nucleic acid of Claim 3, wherein said RNA is an RNA encoding more than one gene product.
- 5. A nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-127, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive bases of one of SEQ ID NOs: 1-127.
- 6. A vector comprising a promoter operably linked to the nucleic acid sequence of Claims 1,2,3,4, or 5.
- 7. The vector of Claim 6, wherein said promoter is active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
 - 8. A host cell containing the vector of Claim 6 or Claim 7.
- 9. A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 128-298.
- 10. A fragment of the nucleic acid of Claim 8, said fragment comprising at least 10, at
 30 least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 128-298.
 - 11. A vector comprising a promoter operably linked to the nucleic acid of Claim 9 or Claim 10.
- 12. A purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region

within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.

- 13. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-127, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127, the sequences complementary to SEQ ID NOs.: 1-127 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-127 as determined using BLASTN version 2.0 with the default parameters.
- 14. The nucleic acid of Claim 13, wherein said nucleic acid is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Staphylococcus aureus, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
- 15. A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127.
 - 16. A host cell containing the vector of Claim 16.

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- 17. The vector of Claim 15, wherein said polypeptide comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-469.
- 18. A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.
- 19. The polypeptide of Claim 18, wherein said polypeptide comprises a polypeptide comprising one of SEQ ID NOs.: 299-469 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 20. A purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or at least 25% identity to a fragment comprising at least 5, at

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least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127 as determined using FASTA version 3.0t78 with the default parameters.

- 21. The polypeptide of Claim 20, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-469 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-469 as determined using FASTA version 3.0t78 with the default parameters.
- 22. An antibody capable of specifically binding the polypeptide of one of Claims 18-21.
- 23. A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 into a cell.
 - 24. The method of Claim 23, further comprising the step of isolating said polypeptide.
- 25. The method of Claim 23, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 26. A method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.
- 27. The method of Claim 26, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 28. A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:

contacting said gene product with a candidate compound; and determining whether said compound influences the activity of said gene product.

- 29. The method of Claim 28, wherein said gene product is a polypeptide and said activity is an enzymatic activity.
- 30. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.
- 31. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.

32. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transporter activity.

- 33. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transcriptional activity.
- 34. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a DNA replication activity.
 - 35. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a cell division activity.
 - 36. A compound identified using the method of Claim 28.

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- 10 37. The method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
 - 38. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:
 - (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
 - (b) contacting said target with a candidate compound or nucleic acid; and
 - (c) measuring an activity of said target.
- 39. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.
 - 40. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.
- 41. The method of Claim 38, wherein said target is a gene and said activity is transcription of said gene.
 - 42. The method of Claim 38, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.
- 43. The method of Claim 38, wherein said target gene or RNA encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
 - 44. A compound or nucleic acid identified using the method of Claim 38.
 - 45. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising the steps of:

(a) expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

(b) contacting said sensitized cell with a compound; and

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- (c) determining whether said compound inhibits the growth of said sensitized cell.
- 46. The method of Claim 45, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
- 47. The method of Claim 45, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
 - 48. The method of Claim 45, wherein said cell is a Gram negative bacterium.
 - 49. The method of Claim 45, wherein said cell is an E. coli cell.
- 50. The method of Claim 45, wherein said cell is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
- 51. The method of Claim 45, wherein said antisense nucleic acid is transcribed from an inducible promoter.
- 52. The method of Claim 51, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level.
- 53. The method of Claim 45, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.
 - 54. The method of Claim 45, wherein said gene product is a polypeptide.
- 55. The method of Claim 54, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
 - 56. The method of Claim 45, wherein said gene product is an RNA.
 - 57. A compound identified using the method of Claim 45.
- 58. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid

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comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a compound with activity against the product of said gene into a population of cells expressing said gene.

- 59. The method of Claim 58, wherein said compound is an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof.
- 60. The method of Claim 59, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-127 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive bases of one of SEQ ID NOs.: 1-127.
- 61. The method of Claim 58, wherein said population is a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
- 62. The method of Claim 58, wherein said population is a population of Gram negative bacteria.
 - 63. The method of Claim 58, wherein said population is a population of *E. coli* cells.
- 64. The method of Claim 58, wherein said population is a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa,Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis cells or cells from any species falling within the genera of any of the above species.
 - 65. The method of Claim 58, wherein said gene encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
- 66. A preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.
- 67. The preparation of Claim 66, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-127 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.
- 68. A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon.

69. The method of Claim 68, wherein said antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-127 or a proliferation inhibiting portion thereof.

70. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

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- 71. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population.
- 72. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.
- 73. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.
- 74. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.
- 75. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.
- 76. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.
- 77. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid.
- 78. The method of Claim 68, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs.: 1-127.
 - 79. The method of Claim 68 wherein said antisense nucleic acid is an oligonucleotide.
- 80. A method for identifying a gene which is required for proliferation of a microorganism comprising:
 - (a) contacting a microorganism other than *E. coli* with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-127;
 - (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
 - (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.
- 81. The method of Claim 80, wherein said microorganism is a Gram negative 35 bacterium.

82. The method of Claim 80 wherein said microorganism is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.

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- 83. The method of Claim 80, further comprising introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.
- 84. A method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:
 - (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127;
 - (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
 - (c) contacting said first microorganism with a sublethal level of said inhibitory
 nucleic acid, thus sensitizing said first microorganism;
 - (d) contacting the sensitized microorganism of step (c) with a compound; and
 - (e) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 85. The method of Claim 84, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
- 86. The method of Claim 84 wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

87. The method of Claim 84 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene.

88. The method of Claim 84 wherein the step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-127 in said microorganism.

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- 89. The method of Claim 84, wherein said inhibitory nucleic acid is an antisense nucleic acid.
- 90. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.
- 91. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.
 - 92. The method of Claim 84, wherein the step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid comprises directly contacting said microorganism with said inhibitory nucleic acid.
 - 93. The method of Claim 84, wherein the step of contacting the first microorganism with a sublethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said microorganism.
 - 94. The method of Claim 84, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.
 - 95. A compound identified using the method of Claim 84.
 - 96. A method of identifying a compound having the ability to inhibit proliferation comprising:
 - (a) contacting a microorganism other than *E. coli* with a sublethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-127 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
 - (b) contacting the sensitized microorganism of step (a) with a compound; and
 - (c) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 97. The method of Claim 96, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
 - 98. A compound identified using the method of Claim 96.
- 99. A method for identifying a compound having activity against a biological pathway35 required for proliferation comprising:

(a) sensitizing a cell by expressing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, in said cell to reduce the activity or amount of said gene product;

(b) contacting the sensitized cell with a compound; and

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- (c) determining whether said compound inhibits the growth of said sensitized cell.
- 100. The method of Claim 99, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
 - 101. The method of Claim 99, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
 - 102. The method of Claim 99, wherein said cell is a Gram negative bacterium.
 - 103. The method of Claim 99, wherein said Gram negative bacterium is E. coli.
 - 104. The method of Claim 99, wherein said cell is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Campylobacter jejuni, Candida albicans, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Saccharomyces cerevisae, Salmonella cholerasuis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, and Yersinia pestis or any species falling within the genera of any of the above species.
 - 105. The method of Claim 99, wherein said antisense nucleic acid is transcribed from an inducible promoter.
 - 106. The method of Claim 99, further comprising contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level.
 - 107. The method of Claim 99, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.
 - 108. The method of Claim 99, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
 - 109. A compound identified using the method of Claim 99.
 - 110. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

(a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127;

(b) contacting said cell with a compound; and

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- (c) determining whether said compound reduces proliferation of said contacted cell.
- 111. The method of Claim 110, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.
- 112. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.
- 113. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a microorganism.
 - 114. The method of Claim 110, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.
- 115. The method of Claim 114, wherein said mutation is a temperature sensitive mutation.
 - 116. The method of Claim 110, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
 - 117. A compound identified using the method of Claim 110.
 - 118. A method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127, said method comprising:
 - (a) expressing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;
 - (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
 - (c) determining whether said cell is sensitive to said compound.
- 119. The method of Claim 118, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid and wherein said gene or gene product

lies in the same pathway on which said compound acts if said cell expressing said sublethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sublethal level of said antisense nucleic acid.

- 120. The method of Claim 118, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469
- 121. A method for determining the biological pathway on which a test compound acts comprising:
 - (a) expressing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
 - (b) contacting said cell with said test compound; and
 - (c) determining whether said cell is sensitive to said test compound.
- 122. The method of Claim 121, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.
 - 123. The method of Claim 121, further comprising:

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- (d) expressing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and
- (e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.
- 124. A purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127.
 - 125. A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.
- 126. A compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-127 to inhibit proliferation.
 - 127. A method for manufacturing an antibiotic comprising the steps of:

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screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127; and manufacturing the compound so identified.

- 128. The method of Claim 127, wherein said screening step comprises performing any one of the methods of Claims 28, 38, 45, 96, 99 and 110.
- 129. A method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-127 to said subject.
- 130. The method of Claim 129 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.
- 131. The method of Claim 129, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-469.

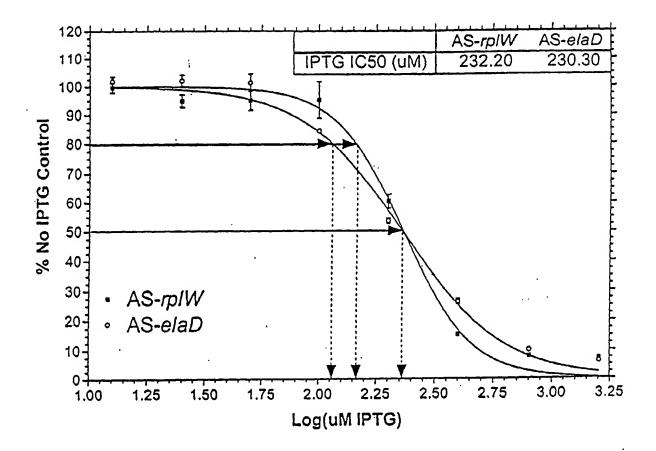


Figure . \

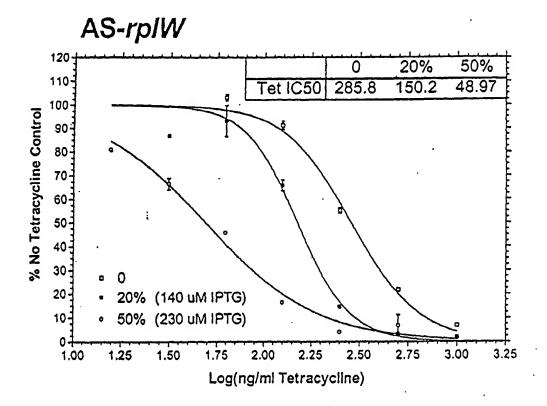


Figure & A

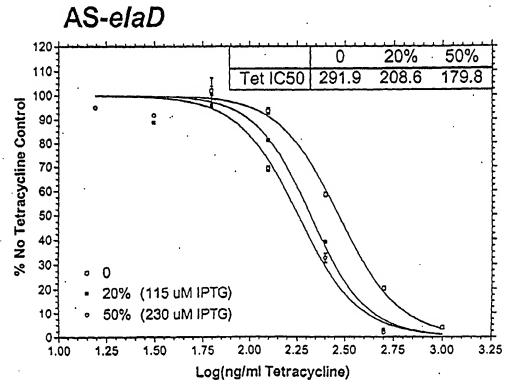


Figure aB

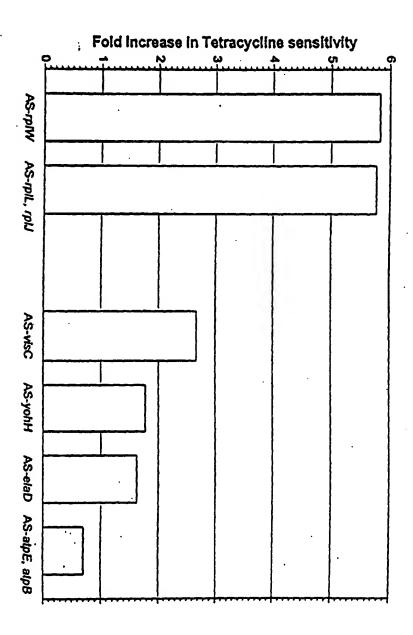


Figure 3

SEQUENCE LISTING

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  atcacctgct tatcagcgcc tttcagcacg atttcagtct gagtcggaca ttcagcagtg
  atacccgcag gcagctgatg gtcaacagga tgagagaaac ccagagacag gttaatcaca
                                                                         360
  ttgcctttaa ccgctgcacg gtaacctaca ccaaccagct gcagcttctt agtgaagcct
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  teggtaacac egataaccat tgagtteage agggeaegeg eggtaceage et
                                                                         172
  <210> 10
  <211> 165
  <212> DNA
  <213> Escherichia coli 🕟
  <400> 10
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  agtotgacga ccgctggcgg cgttgatcac cgcagtacgc acggcatacc agaaagcgga
                                                                         120
  catctgcggg atgttcggca tgatttcacc tttctgggcg ttttc
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  <210> 11
  <211> 328
  <212> DNA
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<213> Escherichia coli

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<220>
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<222> (1) ... (328)
<223> n = A, T, C or G
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                                                                    120
                                                                    180
actgccttcc agcatctccg tcatccagct aaacagttgg ttgacgttct tcatgcgcat
240
                                                                    300
gatcagatca cgcaccgcgg caatcggctc ccgctccgcc agacgctgga tttctgccaa
                                                                    328
ccagtgagtg aagcgggtca atgcttca
<210> 12
<211> 332
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<213> Escherichia coli
<400> 12
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ttttctgtag cgaaactaat atccagtgtc cgccagtatt tatggggaat aactggactt
                                                                    120
catteggeca tgatggateg etettaatat ttteattgag agegtettee aggtgagtte
                                                                    180
tggtggagta ggggacgtag agaccagtag gataattgac ttgagtattt tttgcattag
                                                                    240
                                                                    300
cggcgatctt ctgaagatag caagctattt catctgtggt taattgacga tttttatccc
                                                                    332
agaagtttgt accatcactc agttcattat tc
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<211> 132
<212> DNA
<213> Escherichia coli
<400> 13
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tcatgtgatt tgaggggga gttggttgcg atatgtgcca gattatataa ttttaaacaa
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                                                                    132
gcatttttga ta
<210> 14
<211> 265
<212> DNA
<213> Escherichia coli
<400> 14
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cctagtgcac gcaatgagtt gaatatgacg cattttattt gtagtttatt attttttta
                                                                    120
                                                                    180
tttactattt tctgtagcga aactaatatc cagtgtccgc cagtatttat ggggaataac
tggacttcat tcggccatga tggatcgctc ttaatatttt cattgagagc gtcttccagg
                                                                    240
                                                                    265
tgagttctgg tggagtaggg gacgt
<210> 15
<211> 665
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1)...(665)
<223> n = A, T, C or G
<400> 15
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<210> 17 <211> 246 <212> DNA <213> Escherichia coli	
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<210> 18 <211> 208 <212> DNA <213> Escherichia coli	
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<210> 19 <211> 159 <212> DNA <213> Escherichia coli	
<400> 19 tatgtaagcg gcaaacgaat ggggtaaaca tgccgatttt ttagtaaata tttcgagagg gatatgtttc taatgctaag aaaaaaggtg ccgtagcacc tttttaatag agaggttttg ttaccacaca gcagccagca gcgtatgcga gtccggtac	60 120 159

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<210> 20
<211> 294
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
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<223> n = A, T, C or G
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tggattttca tttgcacttg nctcttcgat cgccttaaca aaatgctgct tgccttgctt
                                                                        120
gcgccggtgc gcttctacng gattgnccgg cgcgatagaa aatcgcttgc ctaagcccgn
                                                                        180
cccctgcaca acctggggtn tattcacttg cgccaggttt tcttgggcgt cacgcccgcc
                                                                        240
aaccggcaaa agactggcga tgtcccgatg gcaatacccg cttttaacgc tttt
                                                                        294
<210> 21
<211> 129
<212> DNA
<213> Escherichia coli
<400> 21
tcqqqttcaa ttttcaaqga acatccaqcq qggaggtaaa cgatacgtgg taattttggt
                                                                         60
                                                                        120
gattttcatt gcactgcctc tcgatacgcc ttaacaaatg ctgctgcctg ctgcgcggtg
                                                                        129
cgctctacg
<210> 22
<211> 151
<212> DNA
<213> Escherichia coli
<400> 22
ctcctgtatc tatattctaa ttaaaaaagtt aaaaacgtta acggcttatg cgtaccgcag
                                                                         60
gcacgcgatt accaggccca gatcgccttt ggaaaccatg gctttcggac gcaggtgacg
                                                                        120
tttacgtttg gtcgcttttt tggtcagaat g
                                                                        151
<210> 23
<211> 579
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1)...(579)
<223> n = A, T, C or G
<400> 23
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aagaaatacc gttctgacgt gctgctgcgt tgatacgcgc aatccacagt tgacggaact
                                                                        120
                                                                        180
gacgettacg ttgacgacgg teacggtaag catactgace agetttgata acageetgga
aggcaacgcg gtatacgcga gaacgcgcac cgtagtagcc tttagcttgt ttcaaaattt
                                                                        240
tcttgtgacg tgcacgtgca ataacaccac gttttacgcg agccatatgt gctctcctgt
                                                                        300
                                                                        360
atctatattc taattaaaaa qttaaaaacg ttaacggctt atgcgtacgg caggcacgcg
                                                                        420
attaccaqqc ccaqatcgcc tttggaaacc atggctttcg gacgcaggtg acgtttacgt
                                                                        480
ttggtcgctt ttttggtcag aatgtgacgc aggttagcgt gcttgtgctt aaaaccacct
                                                                        540
ttaccggttt ttttgaagcg cttagcagca ccgcgtacgg tcttaatttt tggcatttta
                                                                        579
ataacttnca cttcgcattg gtaataaacg aaacaaagg
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<210> 24
<211> 222
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature
<222> (1)...(222)
<223> n = A, T, C or G
<400> 24
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                                                                        60
gttngaggac agttttaata aagttacaat caccgcgata aacgtaacca atttttagca
                                                                       120
actaaacagg ggaaaacaat tacagatttt tatctttcga ttacgatttt tggtttattt
                                                                       180
                                                                       222
cttgatttat gaccgagatc ttacttttgt tgcgcaattg ta
<210> 25
<211> 278
<212> DNA
<213> Escherichia coli
<400> 25
ggagagtttg cagtcattta aaaggtaaca tgacaatgca tgatgaatat aacaacatat
                                                                        60
gatgttatgt aatgtgggag gaaagatcac aaaatttcgc acaggatcgc gctgtggcta
                                                                        120
                                                                        180
atggatgtag ttatcaaatt gaatttaaag tgaaaatatt tttacgggcg ggggcaagaa
ggacatataa acaaatacgc cctcggaaaa tccagagggc gtcgggcaat taaaccggtg
                                                                        240
ttagccgatt tctgtcagag acttactgtg cagtagga
                                                                        278
<210> 26
<211> 156
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1) ... (156)
<223> n = A, T, C or G
<400> 26
tgaaatncga ccgaaggtag tttcggaaac agtcagcgcg ctctgcgcgt ctttcaatac
                                                                         60
                                                                        120
taattccatt gctatctcct tacgccttca cagctggttt aacgatcagg tcgctaccgg
ttgcacccgg gacagcacct ttaaccagca gcaggt
                                                                        156
<210> 27
<211> 143
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature '
<222> (1)...(143)
<223> n = A, T, C or G
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                                                                         60
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atcaggtcgc tccggntgcc ccgggacagc acctttaacc agcagcaggt tgcgctcagc
                                                                        120
                                                                        143
gtcaacgcgt actacgtcaa ggc
<210> 28
<211> 266
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<212> DNA
<213> Escherichia coli
<400> 28
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ttcaatacta attccattgc tatctcctta cgccttcaca gctggtttaa cgatcaggtc
                                                                       120
gctaccggtt gcacccggga cagcaccttt aaccagcagc aggttgcgct cagcgtcaac
                                                                       180
gcgtactacg tcaaggctct gaacggttac acgttcgtta cccatctgac ctgccatttt
                                                                       240
                                                                       266
cttqcctttq aacactttqc ccggag
<210> 29
<211> 535
<212> DNA
<213> Escherichia coli
<400> 29
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                                                                        60
teggaaacag teagegeget etgegegiet ticaatacta attecatige tateteetta
                                                                       120
cgccttcaca gctggtttaa cgatcaggtc gctaccggtt gcacccggga cagcaccttt
                                                                       180
aaccagcagc aggttgcgct cagcgtcaac gcgtactacg tcaaggctct gaacggttac
                                                                       240
acgttcgtta cccatctgac ctgccatttt cttgcctttg aacactttgc ccggagtctg
                                                                       300
qttctqaccq ataqaacccq gaacqcggtq agacaaggag ttaccgtgag tagcgtcctg
                                                                       360
                                                                       420
qqtacqqaaq ttccaqcqct taacqqtacc tgcqaaacct ttacctttag aggtgccagt
                                                                       480
tacgtcaact tttttaacgt cagcaaacag ttcaacgcta atgctctgac ctacagtgaa
ctcttcgcct tcagccaggc ggaattccca cagaccacgg ccagcttcta cgcca
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<210> 30
<211> 223
<212> DNA
<213> Escherichia coli
<400> 30
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cagaccacgg ccagcttcta cgccagcttt agcgaagtgg ccagcttcag gcttggtcac
                                                                       120
acggttaget tttttageac cggtggtcac ctgaatagea cggtagecat cgttagecag
                                                                       180
                                                                       223
gtctttaacc tgagtaacgc ggtttgcttc aacttcgatt acg
<210> 31
<211> 225
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature
<222> (1)...(225)
<223> n = A, T, C or G
<400> 31
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                                                                        60
ttaacgatca ggtcgctacc ggntgcaccc gggacagcac ctttaaccaa cagcangntg
                                                                       120
                                                                       180
cqctcaacqt caacqcqtac tacqtcaaqq ctctgaacqg gtacacqttc gttacccatn
                                                                       225
tgacctgnca ttttcttgcc tttgaacact ttgcccggag tctgg
<210> 32
<211> 341
<212> DNA
<213> Escherichia coli
<400> 32
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                                                                        60
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ggacagcacc tttaaccagc agcaggttgc gctcagcgtc aacgcgtact acgtcaaggc
                                                                       120
tctgaacggt tacacgttcg ttacccatct gacctgccat tttcttgcct ttgaacactt
                                                                       180
tgcccggagt ctggttctga ccgatagaac ccggaacgcg gtgagacaag gagttaccgt
                                                                       240
gagtagegte etgggtaegg aagtteeage gettaaeggt acetgegaaa cetttacett
                                                                       300
tagaggtgcc agttacgtca actttttaa cgtcagcaaa c
                                                                       341
<210> 33
<211> 176
<212> DNA
<213> Escherichia coli
<400> 33
aacaacaacc tggtgaacca gcgcttcgtt gaaatcacga ccgaaggtag tttcggaaac
                                                                        60
agtcagegeg ctctgegegt ctttcaatac taattccatt getateteet taegeettea
                                                                       120
                                                                       176
cagetggttt aacgatcagg tegetacegg ttgcaceegg gacageacet ttaace
<210> 34
<211> 241
<212> DNA
<213> Escherichia coli
<400> 34
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                                                                        60
aatactaatt ccattgctat ctccttacgc cttcacaget ggtttaacga tcaggtcgct
                                                                       120
accggttgca cccgggacag cacctttaac cagcagcagg ttgcgctcag cgtcaacgcg
                                                                       180
tactacgtca aggetetgaa eggttacacg ttegttacec atetgacetg ceattttett
                                                                       240
                                                                       241
<210> 35
<211> 224
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature
<222> (1)...(224)
<223> n = A, T, C or G
<400> 35
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                                                                        60
gtggctccct caagccactt cctttagaag cacaaccttg cttctaacta tataaacctt
                                                                       120
ctgttatata ttacccttta tttttggggg cgtctcaacg ccccattttt aataattttt
                                                                       180
agtaaacaat tggcatatta attagagtta ttaacaacga tatc
                                                                       224
<210> 36
<211> 413
<212> DNA
<213> Escherichia coli
<400> 36
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                                                                        60
attaaaagcc cgaaaatttt actcattttt gcgggaattg caatcaacag ttgctaactc
                                                                       120
tgctgtaaaa ggccgtcggc ggtgcagcca gtttggtgcc ggagtgcgcg cagtcaccgg
                                                                       180
                                                                       240
agcgtacacg cagtacgtga ggatgacgag cacatcccgg tgccaaaatg gcaaacaagc
caggccgatt agcgaccagg gaagcctggg ggcatcatac ccttcatgct tctcatcatc
                                                                       300
ttcgccattc cgcccttctt cattttcttc atcatgcgct gcatgtcgtc gaactgtttc
                                                                       360
agaagacggt taacgtcctg cacctgcata ccgcaaccgg cagcaatacg gcg
                                                                       413
<210> 37
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<211> 509

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<210> 38 <211> 149 <212> DNA <213> Esch	erichia col:	i				
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<210> 39 <211> 118 <212> DNA <213> Esch	erichia col:	i				
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<210> 40 <211> 147 <212> DNA <213> Esch	erichia col:	i				
ttaatgtgat		gcgttctttt	gagaattaat ttccttcaat			60 120 147
<210> 41 <211> 224 <212> DNA <213> Esch	erichia col	i				
gaattaatat ccttcaattg	gaaactgcaa cgacaaatgt	taaattcttt aatactttgg	agaacggctt aatgtgatac ttaatgattg ttaccttcac	aagcctgggc gttggtcgtt	gttctttttt	60 120 180 224
<210> 42 <211> 506 <212> DNA <213> Esch	erichia col	i				
<400> 42						

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cgggagaatt tttttccttc aaacactgac caatattaga tgaaagcagt aatttttagt tacagcctgg	aatatgaaac aattgcgaca gtcgtaaaca tgcattctgc attgcaatac atattctata	tcatccctgg tgcaataaat aatgtaatac cccggtatag cccatcagga agcagcgcgc gtcacgctat aattgcgcca attaag	tctttaatgt tttggttaat cggggttacc aggtatggtc aaaacgtggc gcttcctgcg	gatacaagcc gattggttgg ttcactgtac atattcaacg gatacgggtc gaattatatc	tgggcgttct tcgtttacat cggctgagat agttcagcac agatgatgat cttgcctgat	60 120 180 240 300 360 420 480 506
<210> 43 <211> 184 <212> DNA <213> Esche	erichia col	· i				
tgagggataa	tttccqtcaa	atccagacgt attgaggcaa atcgggagaa	ttgccgagcg	tttcatccct	ggcaagcaga	60 120 180 184
<210> 44 <211> 327 <212> DNA <213> Esche	erichia col	i			•	
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<210> 45 <211> 215 <212> DNA <213> Esch	erichia col	i				
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<210> 46 <211> 121 <212> DNA <213> Esch	erichia col	i				
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<210> 47 <211> 160 <212> DNA <213> Esc		i				
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<210> 48 <211> 195 <212> DNA <213> Esc		i				
cgcagctta	a tttaaactgt t caggtgaagt a ataagataaa a gcgaa	aataattatt	ctcaataatt	aactggagag	gggaatatta	60 120 180 195
<210> 49 <211> 167 <212> DNA <213> Esc		i				
gtaataatt	t tcacaaatag a ttctcaataa g ccgatagata	ttaactggag	aggggaatat	taacgataga		60 120 167
<210> 50 <211> 226 <212> DNA <213> Esc		i				
aataattaa	t gatattaagg g gttaggaatg c tggagaggg t ccgaagccga	tgatatccgc aatattaacg	agcttatcag atagaaaata	gtgaagtaat agataaacaa	aattattctc	60 120 180 226
<210> 51 <211> 185 <212> DNA <213> Esc		i				
tgttctgag	e tgtgeggata g ttateaette a tetetgeeag	aatctggtgc	gggtaggtat	ccagccggta	gagtttcgcc	60 120 180 185
<210> 52 <211> 18 <212> DNI <213> Esc		i				
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tgctattaat taaccgttaa cattaat	tttatactgt tgatggcgaa	tcaagcatgt acttcatcaa	tatgtctggc tattaattcg	tgaagccaat taaagcatct	ttagccacag atctctgtat	120 180 187
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-14-

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                                                                       240
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agacgagcgc ggcctttagc acgacgacgt gccagaacct gacgaccatt tttagtagcc
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gtg Val	gaa Glu 50	aat Asn	gac Asp	ggt Gly	ggt Gly	tct Ser 55	ctg Leu	gaa Glu	gcc Ala	atc Ile	gcc Ala 60	aaa Lys	aaa Lys	tac Tyr	aac Asn	192
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cca Pro	gat Asp	gcg Ala	ccg Pro 100	cgc Arg	gaa Glu	ggc Gly	att Ile	gtg Val 105	atc Ile	aac Asn	att	gcg Ala	gag Glu 110	ctg Leu	cgt Arg	336
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acc Thr 145	gtt	tca Ser	gac Asp	aaa Lys	cgt Arg 150	gca Ala	aac Asn	cca Pro	acc Thr	tgg Trp 155	Thr	cca Pro	acg Thr	gca Ala	aac Asn 160	480
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gco Ala	tat Tyr	ggc Gly 195	Gly	gtt	tat Tyr	ttg Leu	Ctt Leu 200	His	ggt	acg Thr	aac Asn	gcc Ala 205	Asp	ttc Phe	ggc Gly	624
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ato Ile 225	. Lys	aca Thr	t ctc	ttt Phe	ago Ser 230	Gln	gto Val	acc Thr	cca Pro	ggc Gly 235	Thr	aaa Lys	gtg Val	aat Asn	atc Ile 240	720
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1056

cct cca tta tca cct gca acg atg aat ttg cta atg gca att ggt cag

Pro Pro Leu Ser Pro Ala Thr Met Asn Leu Leu Met Ala Ile Gly Gln

			340					345					350			
aat Asn	cac His	caa Gln 355	ctt Leu	acg Thr	caa Gln	ctg Leu	atg Met 360	att Ile	caa Gln	ctc Leu	cag Gln	aaa Lys 365	atg Met	cca Pro	gaa Glu	1104
cta Leu	cat His 370	aga Arg	aca Thr	gaa Glu	atg Met	ttg Leu 375	act Thr	gcc Ala	tat Tyr	aat Asn	agt Ser 380	att Ile	aac Asn	ctg Leu	cca Pro	1152
ggt Gly 385	tta Leu	tat Tyr	ttg Leu	gct Ala	ata Ile 390	aat Asn	tat Tyr	ggt Gly	aat Asn	gcg Ala 395	gat Asp	atc Ile	gtt Val	gag Glu	act Thr 400	1200
att Ile	ttc Phe	aat Asn	tca Ser	ttg Leu 405	tca Ser	gaa Glu	aca Thr	gga Gly	tat Tyr 410	gaa Glu	gga Gly	tta Leu	ctc Leu	tcg Ser 415	aaa Lys	1248
aaa Lys	aat Asn	ctc Leu	atg Met 420	cat His	att Ile	ctg Leu	gag Glu	gca Ala 425	aaa Lys	gat Asp	aaa Lys	aat Asn	ggt Gly 430	ttt Phe	tct Ser	1296
gga Gly	tta Leu	ttt Phe 435	tta Leu	gcg Ala	ata Ile	tca Ser	cgt Arg 440	aag Lys	gat Asp	aaa Lys	aat Asn	gtt Val 445	gta Val	acc Thr	tcg Ser	1344
att Ile	ctg Leu 450	aac Asn	gcc Ala	tta Leu	cct Pro	aaa Lys 455	ctg Leu	gcc Ala	gca Ala	aca Thr	cat His 460	cat His	tta Leu	gat Asp	aac Asn	1392
gaa Glu 465	caa Gln	gtg Val	tat Tyr	aaa Lys	ttc Phe 470	ctg Leu	agt Ser	gcc Ala	aaa Lys	aat Asn 475	aga Arg	acg Thr	tcc Ser	agc Ser	cat His 480	1440
gtt Val	tta Leu	tac Tyr	cat His	gtt Val 485	atg Met	gcg Ala	aat Asn	ggt Gly	gat Asp 490	gcc Ala	gac Asp	atg Met	ctg Leu	aaa Lys 495	att Ile	1488
gtt Val	ttg Leu	aac Asn	gcg Ala 500	tta Leu	cct Pro	ttg Leu	tta Leu	att Ile 505	cgc Arg	aca Thr	tgt Cys	cat His	ttg Leu 510	act Thr	aaa Lys	1536
gaa Glu	cag Gln	gta Val 515	Leu	gat Asp	ctc Leu	ctg Leu	aag Lys 520	gca Ala	aag Lys	gat Asp	ttt Phe	tat Tyr 525	ggt Gly	tgc Cys	cca Pro	1584
gga Gly	cta Leu 530	tat Tyr	ctg Leu	gcg Ala	atg Met	caa Gln 535	aat Asn	gga Gly	cat His	agc Ser	gat Asp 540	atc Ile	gtg Val	aaa Lys	gtt Val	1632
att Ile 545	ctt Leu	gaa Glu	gca Ala	ttg Leu	ccc Pro 550	agc Ser	cta Leu	gcc Ala	cag Gln	gaa Glu 555	att Ile	aac Asn	att Ile	tca Ser	gct Ala 560	1680
tcc Ser	gat Asp	att Ile	gta Val	gat Asp 565	Leu	ctg Leu	acc Thr	gct Ala	aaa Lys 570	Ser	ctt Leu	gcg Ala	cgc Arg	gac Asp 575		1728
ggt Gly	ttg Leu	ttt Phe	atg Met	gcc Ala	atg Met	cag Gln	cgc Arg	gga Gly	cac His	atg Met	aac Asn	gtt Val	att Ile	aat Asn	act Thr	1776

WO 01/34810 PCT/US00/30950 .

•	580		5	85			590			
att ttt aac Ile Phe Asn 595	gca tta Ala Leu	ccc act Pro Thr	ctg t Leu P 600	tt aat Phe Asn	acg tt Thr Ph	tt aaa ne Lys 605	ttc g Phe <i>F</i>	at Asp	aaa Lys	1824
aaa aat atg Lys Asn Met 610	aag ccc Lys Pro	ctc ctc Leu Leu 615	ctg g Leu A	gca aat Ala Asn	Asn Se	ct aat er Asn 20	gaa t Glu 1	cat Tyr	ccc Pro	1872
ggt ttg ttt Gly Leu Phe 625	tca gcg Ser Ala	ata cag Ile Gln 630	cat a His L	aaa caa Lys Gln	caa aa Gln As 635	at gtt sn Val	gta q Val (Glu	acg Thr 640	1920
gtt tat ctt Val Tyr Leu	gct tta Ala Leu 645	tct gac Ser Asp	cat g His A	gca cgc Ala Arg 650	ctg ti Leu Pl	tt gga he Gly	Phe :	acc Thr 655	gct Ala	1968
gaa gat att Glu Asp Ile	atg gat Met Asp 660	ttt tgg Phe Trp	Gln H	cac aaa His Lys 665	gcc co Ala P	ca caa ro Gln	aaa t Lys t	tac Tyr	tct Ser	2016
gcc ttt gag Ala Phe Glu 675	Leu Ala	ttt gaa Phe Glu	ttt g Phe 6 680	ggt cac Gly His	cgg g	tt att al Ile 685	gct (Ala (gaa Glu	tta Leu	2064
atc ctt aat Ile Leu Asr 690	aca tta Thr Leu	aat aag Asn Lys 695	atg o	gct gaa Ala Glu	Ser P	tt ggc he Gly 00	ttt Phe	acg Thr	gat Asp	2112
aac cct cga Asn Pro Arq 705	tac att Tyr Ile	gcg gag Ala Glu 710	aaa a Lys A	aat tat Asn Tyr	atg g Met G 715	aa gct lu Ala	tta Leu	ctc Leu	aaa Lys 720	2160
aaa gca tct Lys Ala Se	ccc cat Pro His 725	Thr Val	cgc t	taa *						2187
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atg gag aa Met Glu Ly	a tcc att s Ser Ile 20	t gtt gtt e Val Val	gct	atc gaa Ile Glu 25	cgt t Arg E	tt gtg Phe Val	aaa Lys 30	cac His	ccg Pro	96
atc tac gg Ile Tyr Gl 3	y Lys Phe	e Ile Lys	g cgt s Arg - 40	acg acc Thr Thr	aaa o	ctg cac Leu His 45	Val	cat His	gac Asp	144

gag Glu	aac Asn 50	aac Asn	gaa Glu	tgc Cys	ggt Gly	atc Ile 55	ggt Gly	gac Asp	gtg Val	gtt Val	gaa Glu 60	atc Ile	cgc Arg	gaa Glu	tgc Cys	192
cgt Arg 65	ccg Pro	ctg Leu	tcc Ser	aag Lys	act Thr 70	aaa Lys	tcc Ser	tgg Trp	acg Thr	ctg Leu 75	gtt Val	cgc Arg	gtt Val	gta Val	gag Glu 80	240
	-	gtt Val	ctg Leu	taa *												255
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gag .Glu	ctg Leu	ctg Leu	aac Asn 20	ctg Leu	ctg Leu	cgt Arg	gag Glu	cag Gln 25	ttc Phe	aac Asn	ctg Leu	cgt Arg	atg Met 30	cag Gln	gct Ala	96
gca Ala	agt Ser	ggc Gly 35	cag Gln	ctg Leu	caa Gln	cag Gln	tct Ser 40	cac His	ctg Leu	ttg Leu	aag Lys	caa Gln 45	gtg Val	cgt Arg	cgc Arg	144
gat Asp	gtc Val 50	gca Ala	cgc Arg	gtt Val	aag Lys	act Thr 55	tta Leu	ctg Leu	aac Asn	gag Glu	aag Lys 60	gcg Ala	ggt Gly	gcg Ala	taa *	192
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aac Asn	cgc Arg	ggt Gly	ctg Leu 20	gcg Ala	cag Gln	ggt Gly	acg Thr	gat Asp 25	Val	agc Ser	ttc Phe	ggc Gly	agc Ser 30	Phe	ggt Gly	96
ctg	aaa	gct	gtt	ggc	cgt	ggt	cgt	ctg	act	gcc	cgt	cag	atc	gaa	gca	144

3	a Val 5	Gly	Arg	Gly	Arg 40	Leu	Thr	Ala	Arg	Gln 45	Ile	Glu	Ala	
gca cgt cg Ala Arg Ar 50	t gct g Ala	atg Met	acc Thr	cgt Arg 55	gca Ala	gtt Val	aag Lys	cgt Arg	caa Gln 60	ggt Gly	aag Lys	atc Ile	tgg Trp	192
atc cgt gt Ile Arg Va 65	g ttc l Phe	ccg Pro	gac Asp 70	aaa Lys	ccg Pro	atc Ile	act Thr	gaa Glu 75	aag Lys	ccg Pro	ctg Leu	gca Ala	gtg Val 80	240
cgt atg gg Arg Met Gl	t aaa y Lys	ggt Gly 85	aaa Lys	ggt Gly	aac Asn	gtg Val	gag Glu 90	tat Tyr	tgg Trp	gtt Val	gcc Ala	ttg Leu 95	att Ile	288
cag ccg gg Gln Pro Gl	t aaa y Lys 100	gtc Val	ctg Leu	tat Tyr	gaa Glu	atg Met 105	gac Asp	ggt Gly	gtt Val	ccg Pro	gaa Glu 110	gag Glu	ctg Leu	336
gcc cgt ga Ala Arg Gl 11	u Ala	ttc Phe	aag Lys	ctg Leu	gca Ala 120	gca Ala	gcg Ala	aaa Lys	ctg Leu	ccg Pro 125	att Ile	aaa Lys	acc Thr	384
acc ttt gt Thr Phe Va 130	a act l Thr	aag Lys	acg Thr	gtg Val 135	atg Met	taa *					•			411
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85		90	95	
gtt cct gca cag atc a Val Pro Ala Gin Ile A 100	ac atc gcc gaa Asn Ile Ala Glu 105	Val Arg Lys Pro	t gaa ctg gad o Glu Leu Asp 110	336
gca aaa ctg gtt gct g Ala Lys Leu Val Ala A 115	gac agc atc act Asp Ser Ile Thr 120	tct cag ctg gad Ser Gln Leu Glo 12	u Arg Arg Val	384
atg ttc cgt cgt gct a Met Phe Arg Arg Ala M 130	atg aag cgt gct Met Lys Arg Ala 135	gta cag aac gca Val Gln Asn Ala 140	a atg cgt cto a Met Arg Leo	3 432 1
ggc gct aaa ggt att a Gly Ala Lys Gly Ile I 145	aaa gtt gaa gtt Lys Val Glu Val 150	agc ggc cgt cto Ser Gly Arg Leo 155	g ggc ggc gcg u Gly Gly Ala 160	ì
gaa atc gca cgt acc g Glu Ile Ala Arg Thr G 165	gaa tgg tac cgc Glu Trp Tyr Arg	gaa ggt cgc gt Glu Gly Arg Va 170	a ccg ctg cad l Pro Leu His 175	528
act ctg cgt gct gac a Thr Leu Arg Ala Asp I 180		Thr Ser Glu Al		
tac ggt gta atc ggc g Tyr Gly Val Ile Gly V 195			y Glu Ile Le	
ggt ggt atg gct gct g Gly Gly Met Ala Ala V 210	gtt gaa caa ccg Val Glu Gln Pro 215	ggaa aaa ccg gc Glu Lys Pro Al 220	t gct cag co a Ala Gln Pro	672
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gtt cgc ctt gtt gct (Val Arg Leu Val Ala) 20	gac ctg att cgc Asp Leu Ile Arg 25	, Gly Lys Lys Va	g tcg cag gc 1 Ser Gln Al 30	t 96 a
ctg gat att ttg acc t Leu Asp Ile Leu Thr '	tac acc aac aag Tyr Thr Asn Lys 40	s Lys Ala Ala Va	a ctg gtc aa l Leu Val Ly 5	g 144 s

aaa gtt ctg gaa tct Lys Val Leu Glu Ser 50	gcc att gct a Ala Ile Ala A 55	aac gct gaa cac Asn Ala Glu His 60	aac gat ggc gct 192 Asn Asp Gly Ala	
gac att gac gat ctg Asp Ile Asp Asp Leu 65	aaa gtt acg a Lys Val Thr L 70	aaa att ttc gta Lys Ile Phe Val . 75	gac gaa ggc ccg 240 Asp Glu Gly Pro 80	
agc atg aag cgc att Ser Met Lys Arg Ile 85	atg ccg cgt g Met Pro Arg A	gca aaa ggt cgt Ala Lys Gly Arg 90	gca gat cgc atc 288 Ala Asp Arg Ile . 95	
ctg aag cgc acc agc Leu Lys Arg Thr Ser 100	His Ile Thr V	gtg gtt gtg tcc Val Val Ser 105	gat cgc tga 333 Asp Arg * 110	
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aag aag gta gag aaa Lys Lys Val Glu Lys 20	gcg gtg gaa a Ala Val Glu S	agc gga gac aag Ser Gly Asp Lys 25	aag ccc ctg cgc 96 Lys Pro Leu Arg 30	
act tgg tcc cgt cgt Thr Trp Ser Arg Arg 35	tca acg atc t Ser Thr Ile I 40	ttt cct aac atg Phe Pro Asn Met	atc ggt ttg acc 144 Ile Gly Leu Thr 45	
atc gct gtc cat aat Ile Ala Val His Asn 50	ggt cgt cag o Gly Arg Gln F 55	cac gtt ccg gta His Val Pro Val 60	ttt gta acc gac 192 Phe Val Thr Asp	
gaa atg gtt ggt cac Glu Met Val Gly His 65	aaa ctg ggt o Lys Leu Gly (70	gaa ttc gca ccg Glu Phe Ala Pro 75	act cgt act tat 240 Thr Arg Thr Tyr 80	
cgc ggc cac gct gct Arg Gly His Ala Ala 85	gat aaa aaa q Asp Lys Lys A	gcg aag aag aaa Ala Lys Lys Lys 90	taa 279 *	
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Met Asn Pro 225	Val Asp	His Pro 230	His Gly	Gly Gly 235		Arg Asn	Phe 240						
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acc cgc agc Thr Arg Ser	aac aag Asn Lys 260	cgt act Arg Thr	gat aaa Asp Lys 265	Phe Ile	gta cgt Val Arg	cgc cgt Arg Arg 270	agc 816 Ser						
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tct gaa aaa Ser Glu Lys	gcg tct Ala Ser 20	act gcg Thr Ala	atg gaa Met Glu 25	ı Lys Sei	aac acc Asn Thi	atc gta Ile Val 30	ctc 96 Leu .						
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aaa ctg ttt Lys Leu Phe 50	gaa gto Glu Val	gaa gto Glu Val	Glu Val	gtt aad Val Asi	acc cto Thr Les 60	g gta gtt 1 Val Val	aaa 192 Lys						
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aaa aaa gct Lys Lys Ala	tac gto Tyr Val	Thr Leu	aaa gaa Lys Glu	ggc car Gly Gli 90	g aat cto n Asn Le	g gac tto 1 Asp Phe 95	e Val						
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-39-

<213> Escherichia coli

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act a	acc Thr	ttc Phe	ggt Gly 20	cgt Arg	gat Asp	ttc Phe	aac Asn	gaa Glu 25	gcg Ala	ctg Leu	gtt Val	cac His	cag Gln 30	gtt Val	gtt Val	96
gtt (Val	gct Ala	tat Tyr 35	gca Ala	gct Ala	ggt Gly	gct Ala	cgt Arg 40	cag Gln	ggt Gly	act Thr	cgt Arg	gct Ala 45	cag Gln	aag Lys	act Thr	144
cgt Arg	gct Ala 50	gaa Glu	gta Val	act Thr	ggt Gly	tcc Ser 55	ggt Gly	aaa Lys	aaa Lys	ccg Pro	tgg Trp 60	cgc Arg	cag Gln	aaa Lys	ggc Gly	192
acc Thr 65	ggc Gly	cgt Arg	gcg Ala	cgt Arg	tct Ser 70	ggt Gly	tct Ser	atc Ile	aag Lys	agc Ser 75	ccg Pro	atc Ile	tgg Trp	cgt Arg	tct Ser 80	240
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aac Asn	aag Lys	aag Lys	atg Met 100	tac Tyr	cgc Arg	ggc Gly	gcg Ala	ctg Leu 105	aaa Lys	agc Ser	atc Ile	ctg Leu	tcc Ser 110	gaa Glu	ctg Leu	336
gta Val	cgt Arg	cag Gln 115	gat Asp	cgt Arg	ctg Leu	atc Ile	gtt Val 120	gtc Val	gag Glu	aag Lys	ttc Phe	tct Ser 125	gta Val	gaa Glu	gcg Ala	384
ccg Pro	aaa Lys 130	act Thr	aag Lys	ctg Leu	ctg Leu	gca Ala 135	cag Gln	aaa Lys	ctg Leu	aaa Lys	gac Asp 140	atg Met	gct Ala	ctg Leu	gaa Glu	432
gat Asp 145	Val	Leu	Ile	Ile	Thr	Gly	Glu	ctg Leu	Asp	Glu	Asn	ctg Leu	ttc Phe	ctg Leu	gct Ala 160	480
gcg Ala	cgc Arg	aac Asn	ctg Leu	cac His 165	Lys	gtt Val	gac Asp	gta Val	cgc Arg 170	gat Asp	gca Ala	act Thr	ggt Gly	atc Ile 175	Asp	528
ccg Pro	gtt Val	agc Ser	ctg Leu 180	Ile	gcc Ala	ttc Phe	gac Asp	aaa Lys 185	gtc Val	gta Val	atg Met	act Thr	gct Ala 190	Asp	gct Ala	576
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cgc Arg	gtt Val	act Thr 35	cag Gln	gtt Val	aaa Lys	gac Asp	ctg Leu 40	gct Ala	aac Asn	gat Asp	ggc Gly	tac Tyr 45	cgt Arg	gct Ala	att Ile	144
cag Gln	gtg Val 50	acc Thr	acc Thr	ggt Gly	gct Ala	aaa Lys 55	aaa Lys	gct Ala	aac Asn	cgt Arg	gtg Val 60	acc Thr	aag Lys	cct	gaa Glu	192
gct Ala 65	ggc Gly	cac His	ttc Phe	gct Ala	aaa Lys 70	gct Ala	ggc Gly	gta Val	gaa Glu	gct Ala 75	ggc Gly	cgt Arg	ggt Gly	ctg Leu	tgg Trp 80	240
gaa Glu	ttc Phe	cgc Arg	ctg Leu	gct Ala 85	gaa Glu	ggc Gly	gaa Glu	gag Glu	ttc Phe 90	act Thr	gta Val	ggt Gly	cag Gln	agc Ser 95	att Ile	288
agc Ser	gtt Val	gaa Glu	ctg Leu 100	ttt Phe	gct Ala	gac Asp	gtt Val	aaa Lys 105	aaa Lys	gtt Val	gac Asp	gta Val	act Thr 110	ggc Gly	acc Thr	336
tct Ser	aaa Lys	ggt Gly 115	aaa Lys	ggt Gly	ttc Phe	gca Ala	ggt Gly 120	acc Thr	gtt Val	aag Lys	cgc Arg	tgg Trp 125	aac Asn	ttc Phe	cgt Arg	384
acc Thr	cag Gln 130	gac Asp	gct Ala	act Thr	cac His	ggt Gly 135	aac Asn	tcc Ser	ttg Leu	tct Ser	cac His 140	Arg	gtt Val	ccg Pro	ggt Gly	432
tct Ser 145	Ile	ggt Gly	cag Gln	aac Asn	cag Gln 150	Thr	ccg Pro	ggc Gly	aaa Lys	gtg Val 155	Phe	aaa Lys	ggc	aag Lys	aaa Lys 160	480
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gtc Val	ccg Pro	ggt Gly 195	/ Ala	acc Thr	ggt Gly	ago Ser	gac Asp 200	Leu	ato Ile	gtt Val	aaa Lys	cca Pro 205	Ala	gtg Val	aag Lys	624

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ctg Leu	atc Ile	gat Asp	caa Gln 20	gca Ala	acc Thr	gcg Ala	gaa Glu	atc Ile 25	gtc Val	gag Glu	act Thr	gcc Ala	aag Lys 30	cgc Arg	act Thr .	96
ggt Gly	gcg Ala	cag Gln 35	gtc Val	cgt Arg	ggt Gly	ccg Pro	atc Ile 40	ccg Pro	ctg Leu	ccg Pro	aca Thr	cgc Arg 45	aaa Lys	gag Glu	cgc Arg	144
ttc Phe	act Thr 50	gtt Val	ctg Leu	atc Ile	tcc Ser	ccg Pro 55	cac His	gtc Val	aac Asn	aaa Lys	gac Asp 60	gcg Ala	cgc Arg	gat Asp	cag Gln	192
tac Tyr 65	gaa Glu	atc Ile	cgt Arg	act Thr	cac His 70	ttg Leu	cgt Arg	ctg Leu	gtt Val	gac Asp 75	atc Ile	gtt Val	gag Glu	cca Pro	acc Thr 80	240
gag Glu	aaa Lys	acc Thr	gtt Val	gat Asp 85	gct Ala	ctg Leu	atg Met	cgt Arg	ctg Leu 90	gat Asp	ctg Leu	gct Ala	gcc Ala	ggt Gly 95	gta Val	288
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	1> C		. (47	10)												
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tgg Trp	tgc Cys	ctg Leu	tgg Trp	gct Ala	gat Asp	gtt Val	gca Ala	gca Ala	aag Lys	cta Leu	agg Arg	tcg Ser	ctt Leu	aaa Lys	cgc Arg	96

-42-

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				ggt Gly												1536

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980 985 990

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cat tta tcc aat gg His Leu Ser Asn Gl	c atg aaa tcg y Met Lys Ser	g aaa tca gtc Lys Ser Val	gat acc cgc agt Asp Thr Arg Ser	ata 4416 Ile

1470 1465 1460 tat cgt gaa ctg ggc gca acg ctg agt tac aac atg cgt ctg ggg aac 4464 Tyr Arg Glu Leu Gly Ala Thr Leu Ser Tyr Asn Met Arg Leu Gly Asn 1475 ggt atg gaa gtt gag ccg tgg ctg aag gcg gct gtg cgc aaa gaa ttt 4512 Gly Met Glu Val Glu Pro Trp Leu Lys Ala Ala Val Arg Lys Glu Phe 1495 1490 gtc gat gat aac cgg gtg aaa gtg aat agt gac ggt aat ttc gtc aat 4560 Val Asp Asp Asn Arg Val Lys Val Asn Ser Asp Gly Asn Phe Val Asn 1515 tat ttg tcg ggc aga cgt gga ata tac cag gca ggt att aaa gcc tca 4608 Tyr Leu Ser Gly Arg Arg Gly Ile Tyr Gln Ala Gly Ile Lys Ala Ser 1530 1525 ttc agc agt acg tta agc ggg cat ctt ggg gtg ggg tat agc cat agt 4656 Phe Ser Ser Thr Leu Ser Gly His Leu Gly Val Gly Tyr Ser His Ser 1545 gee ggt gtg gaa tee eeg tgg aac geg gta get ggt gtg aac tgg teg 4704 Ala Gly Val Glu Ser Pro Trp Asn Ala Val Ala Gly Val Asn Trp Ser 1560 1555 4710 ttc tga Phe * <210> 142 <211> 117 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(117) <400> 142 atg aaa gtt cgt gct tcc gtc aag aaa tta tgc cgt aac tgc aaa atc 48 Met Lys Val Arg Ala Ser Val Lys Lys Leu Cys Arg Asn Cys Lys Ile 10 gtt aag cgt gat ggt gtc atc cgt gtg att tgc agt gcc gag ccg aag 96 Val Lys Arg Asp Gly Val Ile Arg Val Ile Cys Ser Ala Glu Pro Lys 25 30 20 117 cat aaa cag cgc caa ggc tga His Lys Gln Arg Gln Gly * 35 <210> 143 <211> 1332 <212> DNA <213> Escherichia coli

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gta Val 225	tta Leu	gta Val	ttt Phe	gca Ala	gtg Val 230	acg Thr	ttc Phe	ttt Phe	gtt Val	gta Val 235	ttt Phe	gtt Val	gag Glu	cgt Arg	ggt Gly 240	720
caa Gln	cgc Arg	cgc Arg	att Ile	gtg Val 245	gta Val	aac Asn	tac Tyr	gcg Ala	aaa Lys 250	cgt Arg	cag Gln	caa Gln	ggt Gly	cgt Arg 255	cgt Arg	7 <u>.</u> 68
gtc Val	tat Tyr	gct Ala	gca Ala 260	cag Gln	agc Ser	aca Thr	cat His	tta Leu 265	ccg Pro	ctg Leu	aaa Lys	gtg Val	aat Asn 270	atg Met	gcg Ala	816
GJ Å ååå	gta Val	atc Ile 275	ccg Pro	gca Ala	atc Ile	ttc Phe	gct Ala 280	tcc Ser	agt Ser	att Ile	att Ile	ctg Leu 285	ttc Phe	ccg Pro	gcg Ala	864
acc Thr	atc Ile 290	gcg Ala	tca Ser	tgg Trp	ttc Phe	ggg Gly 295	ggc Gly	ggt Gly	act Thr	ggt Gly	tgg Trp 300	aac Asn	tgg Trp	ctg Leu	aca Thr	912
aca Thr 305	att Ile	tcg Ser	ctg Leu	tat Tyr	ttg Leu 310	cag Gln	cct Pro	ggg Gly	caa Gln	ccg Pro 315	ctt Leu	tạt Tyr	gtg Val	tta Leu	ctc Leu 320	9,60,
tat Tyr	gcg Ala	tct Ser	gca Ala	atc Ile 325	atc Ile	ttc Phe	ttc Phe	tgt Cys	ttc Phe 330	ttc Phe	tac Tyr	acg Thr	gcg Ala	ttg Leu 335	gtt Val	1008
ttc Phe	aac Asn	ccg Pro	cgt Arg 340	Glu	aca Thr	gca Ala	gat Asp	aac Asn 345	ctg Leu	aag Lys	aag Lys	tcc Ser	ggt Gly 350	gca Ala	ttt Phe	1056
gta Val	cca Pro	gga Gly 355	Ile	cgt Arg	ccg Pro	gga Gly	gag Glu 360	Gln	acg Thr	gcg Ala	aag Lys	tat Tyr 365	atc Ile	gat Asp	aaa Lys	1104
gta Val	atg Met 370	Thr	cgc Arg	ctg Leu	acc Thr	ctg Leu 375	gtt Val	ggt Gly	gcg Ala	ctg Leu	tat Tyr 380	Ile	acc Thr	ttt Phe	atc Ile	1152
tgc Cys 385	Leu	atc Ile	ccg Pro	gag Glu	ttc Phe 390	Met	cgt Arg	gat Asp	gca Ala	atg Met 395	Lys	gta Val	Pro	ttc Phe	tac Tyr 400	1200
ttc Phe	ggt	ggg	acc Thr	tca Ser 405	Leu	ctt Leu	ato	gtt Val	gtt Val 410	Val	gtg Val	att Ile	atg Met	gac Asp 415	ttt Phe	1248
atg Met	gct Ala	caa Gln	gtg Val 420	Gln	act Thr	ctg Leu	atg Met	atg Met 425	Ser	: agt :Ser	cag Gln	tat Tyr	gag Glu 430	Ser	gca Ala	1296
ttg Leu	aaq Lys	aag Lys 435	: Ala	aac Asr	ctg Lev	aaa Lys	ggc Gly 440	' Tyr	ggc Gly	cga Arg	taa / *	ı				1332

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aaa cgc ctg ggt cgt ggt atc ggt tct ggc ctc ggt aaa acc ggt ggt Lys Arg Leu Gly Arg Gly Ile Gly Ser Gly Leu Gly Lys Thr Gly Gly 20 25 30	96
cgt ggt cac aaa ggt cag aag tot cgt tot ggc ggt ggc gta cgt cgc Arg Gly His Lys Gly Gln Lys Ser Arg Ser Gly Gly Gly Val Arg Arg 35 40 45	144
ggt ttc gag ggt ggt cag atg cct ctg tac cgt cgt ctg ccg aaa ttc Gly Phe Glu Gly Gly Gln Met Pro Leu Tyr Arg Arg Leu Pro Lys Phe 50 55 60	192
ggc ttc act tct cgt aaa gca gcg att aca gcc gaa att cgt ctg tct Gly Phe Thr Ser Arg Lys Ala Ala Ile Thr Ala Glu Ile Arg Leu Ser 65 70 75 80	240
gac ctg gct aaa gta gaa ggc ggt gta gta gac ctg aac acg ctg aaa Asp Leu Ala Lys Val Glu Gly Gly Val Val Asp Leu Asn Thr Leu Lys 85 90 95	. 288
gcg gct aac att atc ggt atc cag atc gag ttc gcg aaa gtg atc ctg Ala Ala Asn Ile Ile Gly Ile Gln Ile Glu Phe Ala Lys Val Ile Leu 100 105 110	336
gct ggc gaa gta acg act ccg gta act gtt cgt ggc ctg cgt gtt act Ala Gly Glu Val Thr Thr Pro Val Thr Val Arg Gly Leu Arg Val Thr 115 120 125	384
aaa ggc gct cgt gct gct atc gaa gct gct ggc ggt aaa atc gag gaa Lys Gly Ala Arg Ala Ala Ile Glu Ala Ala Gly Gly Lys Ile Glu Glu 130 135 140	432
taa *	435
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1				5					10					15		
ctg Leu	ccg Pro	aaa Lys	cac His 20	aag Lys	gca Ala	acg Thr	ctg Leu	ctt Leu 25	ggc Gly	ctg Leu	ggt Gly	ctg Leu	cgt Arg 30	cgt Arg	att Ile	96
ggt Gly	cac His	acc Thr 35	gta Val	gag Glu	cgc Arg	gag Glu	gat Asp 40	act Thr	cct Pro	gct Ala	att Ile	cgc Arg 45	ggt Gly	atg Met	atc Ile	144
aac Asn	gcg Ala 50	gtt Val	tcc Ser	ttc Phe	atg Met	gtt Val 55	aaa Lys	gtt Val	gag Glu	gag Glu	taa *					180
<211 <212)> 14 l> 50 2> DN 3> Es) 4	richi	ia co	oli		٠									
	L> CI	os L)	. (504	1)											•	
ata	0> 14 gct Ala	cac	atc Ile	gaa Glu 5	aaa Lys	caa Gln	gct Ala	ggc Gly	gaa Glu 10	Leu	cag Gln	gaa Glu	aag Lys	ctg Leu 15	atc Ile	48
gcg Ala	gta Val	aac Asn	cgc Arg 20	gta Val	tct Ser	aaa Lys	acc Thr	gtt Val 25	Lys	ggt Gly	ggt Gly	cgt Arg	att Ile 30	ttc Phe	tcc Ser	96
ttc Phe	aca Thr	gct Ala 35	ctg Leu	act Thr	gta Val	gtt Val	ggc Gly 40	Asp	ggt Gly	aac Asn	ggt Gly	cgc Arg 45	gtt Val	ggt Gly	ttt Phe	144
ggt Gly	tac Tyr 50	Gly	aaa Lys	gcg Ala	cgt Arg	gaa Glu 55	Val	cca Pro	gca Ala	gcg Ala	atc Ile 60	Gln	aaa Lys	gcg Ala	atg Met	192
gaa Glu 65	aaa Lys	gcc Ala	cgt Arg	cgc Arg	aat Asn 70	atg Met	att	aac Asn	gtc Val	gcg Ala 75	Leu	aat Asn	aac Asn	ggc Gly	act Thr 80	240
ctg Leu	caa Gln	cac His	cct Pro	gtt Val 85	Lys	ggt Gly	gtt Val	cac His	acg Thr 90	Gly	tct Ser	cgc Arg	gta Val	tto Phe 95	atg Met	288
cag Gln	ccg Pro	gct Ala	Ser 100	Glu	ggt Gly	acc	ggt Gly	ato Ile 105	: Ile	gcc Ala	ggt Gly	ggt Gly	gca Ala 110	Met	cgc Arg	336
gcc Ala	gtt Val	ctg Leu 115	Glu	gtc Val	gct Ala	GJ?	gtt Val 120	His	aac Asr	gtt Val	cto Lev	gct Ala 125	груз	gco Ala	tat Tyr	384
ggt Gly	tcc Ser 130	Thr	aac Asr	ccg Pro	atc Ile	aac Asr 135	va:	g gtt L Val	cgt L Arc	g Ala	act Thi 140	: Ile	gat Asp	ggc Gly	c ctg / Leu	432

gaa aat atg aat tct cca gaa atg gtc gct gcc aag cgt ggt aaa tcc Glu Asn Met Asn Ser Pro Glu Met Val Ala Ala Lys Arg Gly Lys Ser 145 150 155 160	480
gtt gaa gaa att ctg ggg aaa taa Val Glu Glu Ile Leu Gly Lys * 165	504
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aag ctc cag gag ctg ggc gca act cgc ctg gtg gta cat cgt acc ccg. Lys Leu Gln Glu Leu Gly Ala Thr Arg Leu Val Val His Arg Thr Pro 20 25 30	96
cgt cac att tac gca cag gta att gca ccg aac ggt tct gaa gtt ctg Arg His Ile Tyr Ala Gln Val Ile Ala Pro Asn Gly Ser Glu Val Leu 35 40 45	144
gta gct gct tct act gta gaa aaa gct atc gct gaa caa ctg aag tac Val Ala Ala Ser Thr Val Glu Lys Ala Ile Ala Glu Gln Leu Lys Tyr 50 55 60	192
acc ggt aac aaa gac gcg gct gca gct gtg ggt aaa gct gtc gct gaa Thr Gly Asn Lys Asp Ala Ala Ala Ala Val Gly Lys Ala Val Ala Glu 65 70 75 80	240
cgc gct ctg gaa aaa ggc atc aaa gat gta tcc ttt gac cgt tcc ggg Arg Ala Leu Glu Lys Gly Ile Lys Asp Val Ser Phe Asp Arg Ser Gly 85 90 95	288
ttc caa tat cat ggt cgt gtc cag gca ctg gca gat gct gcc cgt gaa Phe Gln Tyr His Gly Arg Val Gln Ala Leu Ala Asp Ala Ala Arg Glu 100 105 110	336
gct ggc ctt cag ttc taa Ala Gly Leu Gln Phe * 115	354
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gta a Val L	aa .ys	atc Ile	aac Asn 20	ggt Gly	cag Gln	gtt Val	att Ile	acg Thr 25	atc Ile	aaa Lys	ggt Gly	aaa Lys	aac Asn 30	ggc Gly	gag Glu	96
ctg a Leu T	ct hr	cgt Arg 35	act Thr	ctc Leu	aac Asn	gat Asp	gct Ala 40	gtt Val	gaa Glu	gtt Val	aaa Lys	cat His 45	gca Ala	gat Asp	aat Asn	144
acc c Thr L	eu 50	acc Thr	ttc Phe	ggt Gly	ccg Pro	cgt Arg 55	gat Asp	ggt Gly	tac Tyr	gca Ala	gac Asp 60	ggt Gly	tgg Trp	gca Ala	cag Gln	192
gct g Ala G 65	ggt Gly	acc Thr	gcg Ala	cgt Arg	gcc Ala 70	ctg Leu	ctg Leu	aac Asn	tca Ser	atg Met 75	gtt Val	atc Ile	ggt Gly	gtt Val	acc Thr 80	240
gaa g Glu G	ggc Sly	ttc Phe	act Thr	aag Lys 85	aag Lys	ctg Leu	cag Gln	ctg Leu	gtt Val 90	ggt Gly	gta Val	ggt Gly	tac Tyr	cgt Arg 95	gca Ala	288
gcg g Ala V	gtt Val	aaa Lys	ggc Gly 100	aat Asn	gtg Val	att Ile	aac Asn	ctg Leu 105	tct Ser	ctg Leu	ggt Gly	ttc Phe	tct Ser 110	cat His	cct Pro	336
gtt g Val A	gac Asp	cat His 115	cag Gln	ctg Leu	cct Pro	gcg Ala	ggt Gly 120	atc Ile	act Thr	gct Ala	gaa Glu	tgt Cys 125	ccg Pro	act Thr	cag Gln	384
act g Thr G	gaa Glu 130	atc Ile	gtg Val	ctg Leu	aaa Lys	ggc Gly 135	gct Ala	gat Asp	aag Lys	cag Gln	gtg Val 140	atc Ile	ggc Gly	cag Gln	gtt Val	432
gca g Ala A 145	gcg Ala	gat Asp	ctg Leu	cgc Arg	gcc Ala 150	tac Tyr	cgt Arg	cgt Arg	cct Pro	gag Glu 155	cct Pro	tat Tyr	aaa Lys	ggc	aag Lys 160	480
ggt g Gly V	gtt Val	cgt Arg	tac Tyr	gcc Ala 165	gac Asp	gaa Glu	gtc Val	gtg Val	cgt Arg 170	Thr	aaa Lys	gag Glu	gct Ala	aag Lys 175	aag Lys	528
aag t Lys	taa *															534

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<213> Escherichia coli

<220>

<221> CDS

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)> 14									- •-						40
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ggt Gly	cag Gln	gcc Ala	gcg Ala 20	aac Asn	aaa Lys	gct Ala	gcg Ala	gtc Val 25	acc Thr	atg Met	cct Pro	tcc Ser	tcc Ser 30	aag Lys	ctg Leu	96
aaa Lys	gtg Val	gca Ala 35	atc Ile	gcc Ala	aac Asn	gtg Val	ctg Leu 40	aag Lys	gaa Glu	gaa Glu	ggt Gly	ttt Phe 45	att Ile	gaa Glu	gat Asp	144
ttt Phe	aaa Lys 50	gtt Val	gaa Glu	ggc Gly	gac Asp	acc Thr 55	aag Lys	cct Pro	gaa Glu	ctg Leu	gaa Glu 60	ctt Leu	act Thr	ctg Leu	aag Lys	192
tat Tyr 65	ttc Phe	cag Gln	ggc Gly	aaa Lys	gct Ala 70	gtt Val	gta Val	gaa Glu	agc Ser	att Ile 75	cag Gln	cgt Arg	gtc Val	agc Ser	cgc Arg 80	240
cca Pro	ggt Gly	ctg Leu	cgc Arg	atc Ile 85	tat Tyr	aaa Lys	cgt Arg	aaa Lys	gat Asp 90	gag Glu	ctg Leu	ccg Pro	aaa Lys	gtt Val 95	atg Met	288
gcg Ala	ggt Gly	ctg Leu	ggt Gly 100	atc Ile	gca Ala	gtt Val	gtt Val	tct Ser 105	acc Thr	tct Ser	aaa Lys	ggt Gly	gtt Val 110	atg Met	act Thr	336
gat Asp	cgt Arg	gca Ala 115	gcg Ala	cgc Arg	cag Gln	gct Ala	ggt Gly 120	ctt Leu	ggt Gly	ggc Gly	gaa Glu	att Ile 125	atc Ile	tgc Cys	tac Tyr	384
_	gcc Ala 130	*														393
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	21> 0		. (30	6)												
ato	00> 1 g gct : Ala	- aac	g caa Glr	tca Ser 5	ato Met	aaa Lys	gca Ala	cgc Arg	gaa Glu	ı Val	aaa . Lys	a cgo s Arg	gta Val	gct L Ala	tta Leu	48
gct Ala	gat a Asp	aaa Lys	tac Tyr 20	Phe	gcg Ala	g aaa a Lys	cgo Arç	g gct g Ala 25	Glu	a cto 1 Leu	g aaa 1 Lys	a gcg s Ala	ato 11e 30	5 116	tct Ser	96
gat Aşı	t gto o Val	g aad L Asi 3!	n Ala	tco Ser	gad Asp	gaa Glu	a gat ı Asp 40	Arc	tgg Tr	g aad o Asr	gct n Ala	gtt a Val	Let	c aaq ı Ly:	g ctg s Leu	144

cag act ctg ccg Gln Thr Leu Pro 50	cgt gat tcc Arg Asp Ser 55	Ser Pro S	Ser Arg Gln 60	cgt aac cgc Arg Asn Arg	tgc 192 Cys
cgt caa aca ggt Arg Gln Thr Gly 65	cgt ccg cat Arg Pro His 70	ggt ttc c Gly Phe I	ctg cgg aag Leu Arg Lys 75	ttc ggg ttg Phe Gly Leu	agc 240 Ser 80
cgt att aag gtc Arg Ile Lys Val	cgt gaa gcc Arg Glu Ala 85	gct atg c Ala Met A	egc ggt gaa Arg Gly Glu 90	atc ccg ggt Ile Pro Gly 95	ctg 288 Leu
aaa aag gct agc Lys Lys Ala Ser 100					306
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atg act gag ttt Met Thr Glu Phe 20	aac tac aat Asn Tyr Asr	tct gtc a Ser Val N 25	atg caa gtc Met Gln Val	cct cgg gtc Pro Arg Val 30	gag 96 Glu
aag atc acc ctg Lys Ile Thr Leu 35	aac atg ggt Asn Met Gly	gtt ggt g Val Gly 0 40	gaa gcg atc Slu Ala Ile	gct gac aaa Ala Asp Lys 45	aaa 144 Lys
ctg ctg gat aac Leu Leu Asp Asn 50	gca gca gca Ala Ala Ala 55	Asp Leu A	gca gca atc Ala Ala Ile 60	tcc ggt caa Ser Gly Gln	aaa 192 Lys
ccg ctg atc acc Pro Leu Ile Thr 65	aaa gca cgo Lys Ala Aro 70	aaa tot o Lys Ser V	gtt gca ggc Val Ala Gly 75	ttc aaa atc Phe Lys Ile	cgt 240 Arg 80
cag ggc tat ccg Gln Gly Tyr Pro	atc ggc tgt Ile Gly Cys 85	aaa gta a Lys Val 1	act ctg cgt Thr Leu Arg 90	ggc gaa cgc Gly Glu Arg 95	Met .
tgg gag ttc ttt Trp Glu Phe Phe 100	Glu Arg Le	atc act a lle Thr 1	att gct gta Ile Ala Val	cct cgt atc Pro Arg Ile 110	cgt 336 Arg
gac ttc cgt ggc Asp Phe Arg Gly 115	ctg tcc gct Leu Ser Ala	aag tot t Lys Ser I 120	ttc gac ggt Phe Asp Gly	cgt ggt aac Arg Gly Asn 125	tac 384 Tyr

agc atg ggt gtc Ser Met Gly Val 130		n Ile Ile 1			
aaa gtc gac cgc Lys Val Asp Arg 145	gtt cgt gg Val Arg Gl 150	t ttg gat a y Leu Asp :	att acc att Ile Thr Ile 155	acc act act Thr Thr Thr	gcg 480 Ala 160
aaa tot gac gaa Lys Ser Asp Glu	gaa ggc cg Glu Gly Ar 165	g Ala Leu :	ctg gct gcc Leu Ala Ala 170	ttt gac ttc Phe Asp Phe 175	ccg 528 Pro
ttc cgc aag taa Phe Arg Lys *					540
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aag gtc att gtt Lys Val Ile Val 35					
gtt ccg gcc ctg Val Pro Ala Leu 50	aac caa co Asn Gln Pr 5	o Gly Gly	atc gtt gaa Ile Val Glu 60	aaa gaa gcc Lys Glu Ala	gct 192 Ala
att cag gtt tcc Ile Gln Val Ser 65					
gac cgt gta ggc Asp Arg Val Gly	ttt aga tt Phe Arg Ph 85	c gaa gac e Glu Asp	ggt aaa aaa Gly Lys Lys 90	gtc cgt ttc Val Arg Phe 95	ttc 288 Phe
aag tot aac agc Lys Ser Asn Ser 100					315
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cgt cgc gta atg Arg Arg Val Met 20				
gca ggc gta ggc Ala Gly Val Gly 35				
cgt ggt aag gtc Arg Gly Lys Val 50				
acc aag aag ggt Thr Lys Lys Gly 65			_	_
ggt aat gct tgt Gly Asn Ala Cys				
acg cgt att ttt Thr Arg Ile Phe 100				
atg aaa att atc Met Lys Ile Ile 115				372
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			aaa atc gaa gaa Lys Ile Glu Glu 30	
ctg gta atc tgg Leu Val Ile Trp 35			tat aac ggt ctc Tyr Asn Gly Leu 45	-

gtc Val	ggt Gly 50	aag Lys	aaa Lys	ttc Phe	gag Glu	aaa Lys 55	gat Asp	acc Thr	gga Gly	att Ile	aaa Lys 60	gtc Val	acc Thr	gtt Val	gag Glu	192
cat His 65	ccg Pro	gat Asp	aaa Lys	ctg Leu	gaa Glu 70	gag Glu	aaa Lys	ttc Phe	cca Pro	cag Gln 75	gtt Val	gcg Ala	gca Ala	act Thr	ggc Gly 80	240
gat Asp	ggc Gly	cct Pro	gac Asp	att Ile 85	atc Ile	ttc Phe	tgg Trp	gca Ala	cac His 90	gac Asp	cgc Arg	ttt Phe	ggt Gly	ggc Gly 95	tac Tyr	288
	caa Gln															336
	aag Lys															384
ctg Leu	att Ile 130	gct Ala	tac Tyr	ccg Pro	atc Ile	gct Ala 135	gtt Val	gaa Glu	gcg Ala	tta Leu	tcg Ser 140	ctg Leu	att Ile	tat Tyr	aac Asn	432
	gat Asp															480
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	caa Gln															576
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	tgg Trp															816
	ccg Pro															864

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Phe Leu Glu Asn Tyr Leu Leu Thr Asp Glu Gly Leu Glu Ala Val Asn 305	960
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-	acg Thr		-	_		-		_	-		_	_				528
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PCT/US00/30950 WO 01/34810

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20		-	25	Gly Lys	30	Val I	Te	
acc aat aaa atc Thr Asn Lys Ile	gee eat e Ala His L	etg atc o	25 cgc ggt	tgc ggt	30 tat cag	gcg c	gg 144	
acc aat aaa atc Thr Asn Lys Ile	Ala His L gtg acc t Val Thr P	etg atc of the second s	25 cgc ggt Arg Gly	tgc ggt Cys Gly gca gcg	tat cag Tyr Gln 45	gcg c Ala A	gg 144 rg aa 192	
acc aat aaa atc Thr Asn Lys Ile 35 cac att gcg gcg	Ala His L gtg acc t Val Thr P cag acg c	etg atc of the sector of the s	25 cgc ggt Arg Gly aat aaa Asn Lys	tgc ggt Cys Gly gca gcg Ala Ala 60 gag gcg	tat cag Tyr Gln 45 cgc gag Arg Glu cgt ggg	gcg c Ala A atg a Met L ctg a Leu M	gg 144 rg aa 192 ys tg 240	
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acc aat aaa atc Thr Asn Lys Ile 35 cac att gcg gcg His Ile Ala Ala 50 gag cgt gta ggg Glu Arg Val Gly 65 atc tcc act ttc	gtg acc t Val Thr P cag acg c Gln Thr L 70 cat acg t His Thr L 85	etg atc of the Item of the Ite	cgc ggt Arg Gly aat aaa Asn Lys cgc aaa Arg Lys ctg gat Leu Asp 90 ttc tcg	tgc ggt Cys Gly gca gcg Ala Ala 60 gag gcg Glu Ala 75 atc atc Ile Ile	tat cag Tyr Gln 45 cgc gag Arg Glu cgt ggg Arg Gly aaa cgc Lys Arg gac gat	gcg c Ala A atg a Met L ctg a Leu M gag t Glu T 95.	gg 144 rg 192 ys 240 et 80 at 288 yr 336	

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355 360 365

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														a+ a	240
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										tca Ser		432
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	c gca y Ala																528
	c tat r Tyr	-		_			-		_	_		_		-			576
	t ccg e Pro																624
	c acg e Thr 210																672
	t ggc u Gly 5																720
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	_		-		gtt Val						-			-		912
	_		_	_ `	ctg Leu 310			_		_	_		_			960
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	G] y												384
	ccg Pro 130	_	_	_			-				 _	_	 432

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ace aaa att ace acg tat cgt tta cct ccc cgc tgg atg ttc ctg aaa 672

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WO 01/34810 PCT/US00/30950-

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	aac Asn 370															1152
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Lys Arg Val Leu Glu Ala Gly 450 455	Gly Ile Ser Ile Leu Gln 460	Pro Asp Leu
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290

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                                                                       96
Ile Val His Gly Lys Tyr Val Pro Gly Ser Pro Leu Pro Ala Glu Ala
             20
gaa ctc tgt gag gag ttt gca acc tcg cgc aac atc atc cgt gag gtg
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Glu Leu Cys Glu Glu Phe Ala Thr Ser Arg Asn Ile Ile Arg Glu Val
         35
ttc cgt tcg ctg atg gcg aag cgg ctg att gaa atg aaa cgt tat cgc
                                                                      192
Phe Arg Ser Leu Met Ala Lys Arg Leu Ile Glu Met Lys Arg Tyr Arg
ggg gcg ttt gtg gca ccg cgt aac cag tgg aat tac ctc gac act gac
                                                                      240
Gly Ala Phe Val Ala Pro Arg Asn Gln Trp Asn Tyr Leu Asp Thr Asp
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gta ctg caa tgg gtg ctg gaa aat gac tac gac cca cgg ctt atc agt
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Val Leu Gln Trp Val Leu Glu Asn Asp Tyr Asp Pro Arg Leu Ile Ser
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gcc atg agc gaa gtg cga aat ctg gtg gaa ccg gcg att gcc cgt tgg
                                                                      336
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aag gcg ctg Lys Ala Leu 65	-			_		_	_		_	-	_		240
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aaa Lys	ttc Phe	cgt Arg	cct Pro 100	ggt Gly	aca Thr	gat Asp	gaa Glu	ggc Gly 105	gac Asp	tat Tyr	cag Gln	gta Val	aaa Lys 110	ctc Leu	cgc Arg	336
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ctt Leu 145	aat Asn	cgc Arg	gtg Val	aaa Lys	gac Asp 150	gat Asp	ttg Leu	caa Gln	gaa Glu	ctg Leu 155	gca Ala	gtg Val	gtc Val	gaa Glu	tcc Ser 160	480
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					aac Asn 230											720
					aaa Lys											768
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Ala	Asp 290	Thr	Thr	Leu	Asn	Asn 295	Gly	Leu	Lys	Asp	Val 300	Pro	Ser	Arg	Leu	
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	atg Met															96
	gca Ala		_	-				-						_		144

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					ggg Gly 70											240
					gct Ala											288
_			-		agc Ser	_	_	-	_						_	336
					gat Asp											384
	_	_			ggc Gly			_			_	_	_			432
					gga Gly 150											480
					ggc Gly											528
					act Thr											576
					gcc Ala											624
					ctg Leu											672
					tct Ser 230											720
					cca Pro											768
ctg Leu	gtg Val	ctc Leu	tac Tyr 260	acc Thr	ctg Leu	ctg Leu	gcg Ala	ctg Leu 265	gtg Val	att Ile	tcc Ser	ggc Gly	ctg Leu 270	atg Met	ccc Pro	816
					aat Asn											864

tgg atc ccc gc Trp Ile Pro Al 290		•	-		-	_		_	912
gcg atg atc gt Ala Met Ile Va 305		Gly Ser							960
ccg cgg ctg ga Pro Arg Leu Gl			Lys A		-			-	1008
ttc ggc cat gt Phe Gly His Va 34	His Pro								1056
ctg caa ggg gc Leu Gln Gly Al 355			Phe I		-	Asp			1104
agc ctg ctg gg Ser Leu Leu Gl 370		-							1152
acc ttc ggc tc Thr Phe Gly Se 385		Trp Cys							1200
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tca agc ctc at Ser Ser Leu Il 42	Leu Val	-		-		_			1296
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		caa Gln															240
_		gcc Ala							_	_					-		288
	•	gat Asp	-	-	-	-			-		-						336
_		gta Val 115				-		-			_	-		-			384
		gcg Ala															432
gaa Glu 145	ttt Phe	agc Ser	att Ile	gat Asp	tat Tyr 150	cag Gln	gcc Ala	gac Asp	tgt Cys	atc Ile 155	tgg Trp	gaa Glu	att Ile	cac His	ctg Leu 160		480
ctg Leu	ctc Leu	tgc Cys	tac Tyr	agc Ser 165	gtg Val	gtg Val	ctg Leu	gag Glu	atg Met 170	atc Ile	acc Thr	cgc Arg	ctc Leu	gcg Ala 175	ccg Pro		528
		gaa Glu														٠	576
		ggt Gly 195															624
ggt Gly	gaa Glu 210	ctg Leu	gcc Ala	agc Ser	cag Gln	tgg Trp 215	ccg Pro	atg Met	att Ile	tat Tyr	acc Thr 220	gtt Val	gct Ala	gcg Ala	ggt Gly		672
ccg Pro 225	ctg Leu	cgt Arg	ccg Pro	ctg Leu	ggt Gly 230	tac Tyr	aaa Lys	gaa Glu	ggc Gly	att Ile 235	gta Val	acg Thr	ctg Leu	atg Met	gaa Glu 240		720
		tgg Trp															768

Gly Pro Leu	gag att Glu Ile 260											816
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aaa cag cgt Lys Gln Arg 290	act gac Thr Asp	aac gtg Asn Val 295	Ile	gtc Val	atc Ile	gat Asp	tac Tyr 300	gcc Ala	gaa Glu	att Ile	tcg Ser	912
caa ggg ctg Gln Gly Leu 305	cac ccg His Pro	tgg ctg Trp Let 310	gca Ala	ccg Pro	ttc Phe	ctg Leu 315	atg Met	ttc Phe	gtg Val	cca Pro	atg Met 320	960
gag tgg ctc Glu Trp Leu	tgc tac Cys Tyr 325	tac cto	tct Ser	att Ile	tac Tyr 330	aaa Lys	gat Asp	cac His	aac Asn	ccg Pro 335	gat Asp	1008
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Pro Glu Thr	Asn Gly Tyr 100		sn Met Met 05	Leu Gly Asp 110	Glu His	
atg cgt cgc Met Arg Arg 115	gaa agc ctc Glu Ser Leu	gac atg at Asp Met II 120	tc aag ctg le Lys Leu	gcg atg gat Ala Met Asp 125	atg gca 38 Met Ala	14
aaa gag atg Lys Glu Met 130	aac gcg ggt Asn Ala Gly	tat acg ct Tyr Thr Le 135	tg att tcc eu Ile Ser	gcc ggc cca Ala Gly Pro 140	cgc ggg 43 Arg Gly	12
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aat aat cat Asn Asn His	gaa gat gtg Glu Asp Val 20	Thr Trp Se	cg tcc att Ser Ser Ile 25	gcc gcc ggt Ala Ala Gly 30	ttt aag 9 Phe Lys	96
	act tca aaa Thr Ser Lys					14
gac gcg atg Asp Ala Met 50	atc att tgc Ile Ile Cys	ggg tgc at Gly Cys Mo 55	itg gcc cgt Met Ala Arg	ctg aaa aag Leu Lys Lys 60	aac aac 19 Asn Asn	€2
agc gat ttg Ser Asp Leu 65	cac gat tta His Asp Leu 70	Leu Val A	gat tat tat Asp Tyr Tyr 75	gta gtc ggt Val Val Gly	atg aca 24 Met Thr 80	40
ttc atg tca Phe Met Ser	ctg gca ggt Leu Ala Gly 85	aag cat to Lys His C	gc tgc tct Cys Cys Ser 90	gat ggt tat Asp Gly Tyr	atc ggg 28 Ile Gly 95	38
aaa agg tta Lys Arg Leu	cag aag gct Gln Lys Ala 100	Glu Gly I.	ata att gaa Ile Ile Glu 105	ggg atg tta Gly Met Leu 110		36
tta gat atc Leu Asp Ile 115	cgg tta gag Arg Leu Glu	atg gat a Met Asp I 120	atc gtt gtt [le Val Val	aat aac tct Asn Asn Ser 125	aat taa 38 Asn *	84

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gaa Glu																144
-					_	gta Val 55					_			-	_	192
aat Asn 65						G1 y ggg										240
						ggc Gly										288
						gta Val										336
						aaa Lys										384
						gtt Val 135										432
						ctg Leu										480
cct Pro	tct Ser	gat Asp	gtt Val	ggt Gly 165	cag Gln	aag Lys	ccg Pro	gta Val	gat Asp 170	atc Ile	gtt Val	aac Asn	gcg Ala	gcg Ala 175	ctg Leu	528
						ttc Phe										576
						gaa Glu										624

cat His	gcg Ala 210	tcg Ser	att Ile	aac Asn	ccg Pro	gtt Val 215	gaa Glu	acc Thr	ctg Leu	ttt Phe	gtg Val 220	gtt Val	gac Asp	gcc Ala	atg Met	672
acc Thr 225	ggt Gly	cag Gln	gat Asp	gcg Ala	gcc Ala 230	aat Asn	acg Thr	gca Ala	aaa Lys	gca Ala 235	ttc Phe	aat Asn	gaa Glu	gcg Ala	tta Leu 240	720
ccg Pro	ctt Leu	acc Thr	ggc Gly	gta Val 245	gtg Val	ttg Leu	acc Thr	aaa Lys	gtg Val 250	gac Asp	ggc Gly	gat Asp	gcc Ala	cgc Arg 255	ggc Gly	768
ggt Gly	gcg Ala	gcg Ala	ctc Leu 260	tct Ser	att Ile	cgt Arg	cac His	atc Ile 265	act Thr	ggc Gly	aaa Lys	ccg Pro	atc Ile 270	aag Lys	ttc Phe	816
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cgc Arg	atc Ile 290	gcg Ala	tcg Ser	cgt Arg	att Ile	ctc Leu 295	ggc Gly	atg Met	ggc Gly	gac Asp	gta Val 300	ct.g ·Leu	tcg Ser	ctg Leu ·	atc Ile	912
gaa Glu 305	gat Asp	atc Ile	gaa Glu	agc Ser	aaa Lys 310	gtt Val	gac Asp	cgc Arg	gcg Ala	cag Gln 315	gca Ala	gag Glu	aaa Lys	tta Leu	gcc Ala 320	960
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atg Met 385	Lys	gag Glu	cgc Arg	gct Ala	aag Lys 390	cca Pro	gaa Glu	atc Ile	atc Ile	aaa Lys 395	ggt Gly	tcg Ser	cgt Arg	aaa Lys	cgc Arg 400	1200
cgt Arg	att Ile	gct Ala	gcc Ala	ggt Gly 405	tgc Cys	ggt Gly	atg Met	cag Gln	gtg Val 410	cag Gln	gac Asp	gtt Val	aac Asn	cgt Arg 415	ctt Leu	1248
ctg Leu	aaa Lys	cag Gln	ttc Phe 420	gac Asp	gac Asp	atg Met	cag Gln	cgc Arg 425	atg Met	atg Met	aag Lys	aaa Lys	atg Met 430	aag Lys	aag Lys	1296
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cgg gga gta cgc agt gcg caa gaa ctg gaa cgc agt gtt aaa ggt atg Arg Gly Val Arg Ser Ala Gln Glu Leu Glu Arg Ser Val Lys Gly Met 35 40 45	144
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gac gcc gac ggc gcg acc agc acg gct cta agc gtg ctg gcg atg cgc Asp Ala Asp Gly Ala Thr Ser Thr Ala Leu Ser Val Leu Ala Met Arg 85 90 95	288
tcg ctt ggt tgc agc aat atc gac tac ctg gta cca aac cgt ttc gaa Ser Leu Gly Cys Ser Asn Ile Asp Tyr Leu Val Pro Asn Arg Phe Glu 100 105 110	336
gac ggt tac ggc tta agc ccg gaa gtg gtc gat cag gcc cat gcc cgt Asp Gly Tyr Gly Leu Ser Pro Glu Val Val Asp Gln Ala His Ala Arg 115 120 125	384
ggc gcg cag tta att gtc acg gtg gat aac ggt att tcc tcc cat gcg Gly Ala Gln Leu Ile Val Thr Val Asp Asn Gly Ile Ser Ser His Ala 130 135 140	432
ggg gtt gag cac gct cgc tcg ttg ggc atc ccg gtt att gtt acc gat Gly Val Glu His Ala Arg Ser Leu Gly Ile Pro Val Ile Val Thr Asp 145 150 155 160	480
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					cgc Arg 245												768
					cgt Arg												816
:					aaa Lys												864
					gct Ala												912
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					ctg Leu												1152
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					ggg Gly 405												1248

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gaa gtg gta Glu Val Val 465												1440
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ggc gaa cgt Gly Glu Arg 51!	η His Le	g aag gt 1 Lys Va	g atg 1 Met 520	Val	gaa Glu	ccg Pro	gtc Val	ggc Gly 525	ggc Gly	ggt Gly	cca Pro	1584
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aac ggc gtc Asn Gly Va 545												1680
ttt cgc ggc Phe Arg Gly	aac cgo Asn Aro 56	g Ser Le	g caa u Gln	att Ile	atc Ile 570	atc Ile	gac Asp	aat Asn	atc Ile	tgg Trp 575	cca Pro	1728
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Phe	Ala	Gln	Ala 20	Asp	Asp	Ala	Ala	Ile 25	Gln	Gln	Thr	Leu	Ala 30	Lys	Met	
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aca Thr	gtt Val 50	ctg Leu	act Thr	aac Asn	agc Ser	ggc Gly 55	gtg Val	ttg Leu	tac Tyr	atc Ile	acc Thr 60	gat Asp	gat Asp	ggt Gly	aaa Lys	192
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gag Glu	atg Met	atc Ile	gtt Val 100	tat Tyr	aaa Lys	gcg Ala	ccg Pro	cag Gln 105	gaa Glu	aaa Lys	cac His	gtc Val	atc Ile 110	acc Thr	gtg Val	336
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aat Asn	ggc Gly 210	Thr	ctt Leu	gtt Val	ccg Pro	ggt Gly 215	Tyr	cag Gln	ccg Pro	ccg Pro	aaa Lys 220	Glu	atg Met	aaa Lys	gaa Glu	672
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<213> Escherichia coli

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				gac Asp												192
				gcc Ala												240
				tat Tyr 85												288
				gct Ala												336
				cag Gln												384
cag Gln	cca Pro 130	ctg Leu	gag Glu	cta Leu	cgc Arg	gat Asp 135	aaa Lys	gcc Ala	atg Met	ctt Leu	gaa Glu 140	gtg Val	ttg Leu	tat Tyr	gct Ala	432
	Gly	Leu	Ārg	gtc Val	Ser	Glu	Leu	Val	Gly	Leu	Thr	Met	Ser	Asp	Ile	480
				ggc Gly 165												528
cgt Arg	ctg Leu	gtg Val	ccg Pro 180	tta Leu	ggt Gly	gaa Glu	gag Glu	gcg Ala 185	gtt Val	tac Tyr	tgg Trp	ctg Leu	gaa Glu 190	acc Thr	tat Tyr	576
ctg Leu	gaa Glu	cat His 195	ggg Gly	cgt Arg	ccg Pro	tgg Trp	ctg Leu 200	ctg Leu	aat Asn	ggt Gly	gtg Val	tca Ser 205	att Ile	gac Asp	gtg Val	624
				cag Gln												672

210				215					220					
cac cgt a His Arg 1 225														720
ctg tca c Leu Ser E														768
cat ggt o			-			-	_		-			_	_	816
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gcg aat caa agc Ala Asn Gln Ser 130		Leu Ala Ph			2
ttc tat cgc ccg Phe Tyr Arg Pro 145			-	_)
gcc ctg aag tgg Ala Leu Lys Trp			u Gly Lys Ala		3
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gtt gaa tat gac Val Glu Tyr Asp 35					4

_		_	cgg Arg		_	•			•	_		-		_		192
_	_	_	gtt Val		_		-							_		240
		_	gca Ala		-			-		-	_	_	_			288
	_		tta Leu 100	-								_				336
			gtt Val													384
	-	-	gaa Glu				_	-		-	-		_	-		432
			ctg Leu													480
			tat Tyr	_			_			-						528
_			tca Ser 180								-	_				576
-			gaa Glu	_			_	-					_			624
	_		cga Arg	_		_	_						_		_	672
			aat Asn													720
-	_	_	cgt Arg										_	_		768
_			gat Asp 260		-	-		_			_			_	-	816
			ttg Leu													864

ggc Gly	gtt Val 290	gcc Ala	aat Asn	acc Thr	aac Asn	gcc Ala 295	aaa Lys	gtc Val	act Thr	att Ile	acg Thr 300	caa Gln	ggt` Gly	ggc Gly	tat Tyr	912
	att Ile															960
	agt Ser															1008
	gat Asp															1056
	atg Met															1104
	tta Leu 370															1152
	tac Tyr															1200
	acc Thr															1248
	tca Ser															1296
atc Ile	ccġ Pro	gat Asp 435	gat Asp	aaa Lys	aca Thr	tac Tyr	cag Gln 440	Gly	caa Gln	agt Ser	tat Tyr	cgt Arg 445	gtt Val	tcc Ser	tgg Trp	1344
	aag Lys 450															1392
cgc Arg 465	tat Tyr	tcg Ser	aca Thr	cag Gln	aat Asn 470	tac Tyr	ctt Leu	ggt Gly	ctt Leu	aat Asn 475	gat Asp	gca Ala	cta Leu	act Thr	cta Leu 480	1440
	gat Asp															1488
	aat Asn															1536
_	ttg Leu						-								gga Gly	1584

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att Ile 545	ggc Gly	tac Tyr	agt Ser	aac Asn	agt Ser 550	aca Thr	tcc Ser	tgg Trp	ggc Gly	agc Ser 555	tac Tyr	agt Ser	gtc Val	agt Ser	gcc Ala 560	1680
cag Gln	cgt Arg	tca Ser	tgg Trp	aat Asn 565	gaa Glu	gac Asp	ggc Gly	gac Asp	act Thr 570	gac Asp	gat Asp	agc Ser	gtt Val	tat Tyr 575	ctt Leu	1728
					att Ile											1776
					att Ile											1824
aat Asn	aac Asn 610	caa Gln	ctc Leu	aac Asn	gtt Val	agc Ser 615	agc Ser	agt Ser	Gjy	tat Tyr	agc Ser 620	gat Asp	aac Asn	.gct Ala	cgc Arg	1872
gtc Val 625	agt Ser	tat Tyr	agc Ser	gtg Val	aat Asn 630	act Thr	ggc Gly	tat Tyr	acg Thr	atg Met 635	aat Asn	aaa Lys	gcc Ala	agc Ser	aaa Lys 640	1920
gat Asp	ttg Leu	agt Ser	tat Tyr	gtt Val 645	ggg Gly	ggt Gly	tat Tyr	gcc Ala	agc Ser 650	tat Tyr	gag Glu	tca Ser	cca Pro	tgg Trp 655	gga Gly	1968
acg Thr	ctg Leu	gca Ala	ggt Gly 660	tca Ser	att Ile	tct Ser	gca Ala	aat Asn 665	agc Ser	gat Asp	aac Asn	agc Ser	cgt Arg 670	caa Gln	gtt Val	2016
tct Ser	ctc Leu	agc Ser 675	acc Thr	gac Asp	ggt Gly	ggt Gly	ttt Phe 680	gta Val	ttg Leu	cat His	agc Ser	ggt Gly 685	gga Gly	ctg Leu	act Thr	2064
					ttt Phe											2112
gct Ala 705	cca Pro	ggt Gly	gct Ala	caa Gln	gga Gly 710	gcg Ala	cga Arg	ata Ile	aat Asn	tat Tyr 715	ggc Gly	aac Asn	agt Ser	act Thr	atc Ile 720	2160
gat Asp	cga Arg	tgg Trp	ggt Gly	tat Tyr 725	ggt Gly	gtc Val	acc Thr	agc Ser	gct Ala 730	ctt Leu	tct Ser	cct Pro	tat Tyr	cat His 735	gaa Glu	2208
aac Asn	cgt Arg	atc Ile	gcg Ala 740	ctg Leu	gat Asp	atc Ile	aac Asn	gat Asp 745	ctt Leu	gag Glu	aac Asn	gat Asp	gtt Val 750	gaa Glu	tta Leu	2256
aaa Lys	agt Ser	acc Thr 755	Ser	gca Ala	gta Val	gct Ala	gta Val 760	Pro	cgt Arg	cag Gln	ggt Gly	tca Ser 765	gtc Val	gtc Val	ttt Phe	2304

Ala Asp Phe Gl 770	a acc gtg u Thr Val			-		_			2352
cga agt gat gg Arg Ser Asp Gl 785									2400
caa ggc aat gt Gln Gly Asn Va			Gly G						2448
cgt ggt att ga Arg Gly Ile Gl 82	u Gln Gln			-	_	_	_		2496
agt aaa ccc gt Ser Lys Pro Va 835			His T		_	r Pro	_	_	2544
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cag taa Gln * 865									2598
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Gly	Arg	Lys	Ile	Asn 85	Lys	Arg	Glu	Trp	Ala 90	Gly	Asn	Ala	Ser	Ala 95	Trp	
	gac Asp		-	_	_	_	_	-								336
	gag Glu															384
	cgg Arg 130															432
ggg Gly 145	ttg Leu	aaa Lys	gaa Glu	cac His	gac Asp 150	Val	att Ile	ggg Gly	caa Gln	agc Ser 155	gtg Val	ttt Phe	aaa Lys	ctg Leu	ttt Phe 160	480
atg Met	agc Ser	cgt Arg	cgt Arg	gaa Glu 165	gct Ala	Ala	gca Ala	tcc Ser	agg Arg 170	cgc Arg	aat Asn	aac Asn	cgt Arg	gta Val 175	ttt Phe	528
ttt Phe	cga Arg	agc Ser	ggc Gly 180	aat Asn	gca Ala	tat Tyr	gaa Glu	gtc Val 185	gaa Glu	ctg Leu	tgg Trp	ata Ile	cca Pro 190	aca Thr	tgt Cys	576
aaa Lys	ggc Gly	cag Gln 195	cgg Arg	ctg Leu	ttt Phe	ctg Leu	ttt Phe 200	cgc Arg	aat Asn	aaa Lys	ttt Phe	gtc Val 205	cac His	agc Ser	ggc Gly	624
agt Ser	ggc Gly 210	aaa Lys	aac Asn	gag Glu	att Ile	ttt Phe 215	tta Leu	atc Ile	tgt Cys	tcc Ser	ggc Gly 220	acc Thr	gac Asp	att Ile	acc Thr	672
gaa Glu 225	gag Glu	cgc Arg	cgc Arg	gct Ala	cag Gln 230	gag Glu	cga Arg	ctg Leu	cgt Arg	att Ile 235	ctg Leu	gca Ala	aat Asn	acc Thr	gac Asp 240	720
agt Ser	atc Ile	acc Thr	gga Gly	ctg Leu 245	ccg Pro	aat Asn	cgt Arg	aac Asn	gca Ala 250	atg Met	cag Gln	gat Asp	tta Leu	atc Ile 255	gat Asp	768
cac His	gct Ala	att Ile	aat Asn 260	His	gca Ala	gat Asp	aac Asn	aat Asn 265	Lys	gtt Val	ggg Gly	gtt Val	gtg Val 270	tat Tyr	ctt Leu	816
gat Asp	ttg Leu	gat Asp 275	Asn	ttc Phe	aaa Lys	aag Lys	gtc Val 280	Asn	gac Asp	gcc Ala	tat Tyr	ggg Gly 285	Cat	ttg Leu	ttt Phe	864
ggt Gly	gac Asp 290	Gln	tta Leu	tta Leu	cgc Arg	gac Asp 295	Val	tca Ser	ttg Leu	gct Ala	att Ile 300	Leu	agc Ser	tgt Cys	ctç Leu	912
gaa Glu 305	His	gac Asp	cag Gln	gtg Val	ttg Leu 310	Ala	cgt Arg	cca Pro	ggt Gly	ggg Gly 315	Asp	gag Glu	ttt Phe	. ctg Leu	gta Val 320	960
ctg	gca	tcc	aac	acc	tca:	caa	ago	gcg	ctg	gaa	gca	atg	gca	tca	cga	1008

Leu	Ala	Ser	Asn	Thr 325	Ser	Gln	Ser	Ala	Leu 330	Glu	Ala	Met	Ala	Ser 335	Arg		
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tat Tyr	acc Thr	agc Ser 355	tgt Cys	tca Ser	gta Val	ggt Gly	att Ile 360	gca Ala	ctc Leu	tct Ser	ccc Pro	gaa Glu 365	cat His	ggt Gly	tca Ser	11	04
gac Asp	agc Ser 370	acg Thr	gct Ala	att Ile	att Ile	cgt Arg 375	cac His	gcc Ala	gac Asp	aca Thr	gca Ala 380	atg Met	tac Tyr	aca Thr	gcg Ala	11	52
aag Lys 385	gaa Glu	ggc Gly	gga Gly	cga Arg	gga Gly 390	caa Gln	ttt Phe	tgc Cys	gtt Val	ttt Phe 395	acc Thr	cca Pro	gaa Glu	atg Met	aat Asn 400	12	00
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ctg Leu	gaa Glu	aac Asn	gat Asp 420	cag Gln	ttg Leu	gtt Val	att Ile	cac His 425	tat Tyr	caa Gln	ccg Pro	aaa Lys	atc Ile 430	acc Thr	tgg Trp	12	96
cgt Arg	ggc Gly	gaa Glu 435	gtg Val	cgc Arg	agt Ser	ctg Leu	gaa Glu 440	gca Ala	cta Leu	gta Val	cgt Arg	tgg Trp 445	cag Gln	tca Ser	cct Pro .		44
	cgt Arg 450															13	92
	ggg Gly															14	40
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tct Ser 545	gtt Val	att Ile	caa Gln	caa Gln	ttt Phe 550	agc Ser	caa Gln	cta Leu	ggt Gly	gcg Ala 555	Gln	gtg Val	cat His	ctg Leu	gat Asp 560	16	80
gat	ttt	ggt	acc	ggc	tac	tct	tca	ctt	tcg	caa	ctg	gcg	cgc	ttt	ccg	17	28

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caa Gln	cct Pro	gtc Val 595	tcg Ser	cag Gln	tca Ser	ctg Leu	gtc Val 600	cgg Arg	gcg Ala	atc Ile	gtc Val	gct Ala 605	gtg Val	gcc Ala	cag Gln	1824
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gat Asp 625	Ala	ttt Phe	tta Leu	acc Thr	aag Lys 630	aac Asn	ggg Gly	atc Ile	aat Asn	gag Glu 635	cgg Arg	caa Gln	gga Gly	ttt Phe	ttg Leu 640	1920
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	t tcq e Sei	g gco r Ala	ago a Ser 20	: Ala	cat His	gct Ala	gcc Ala	gga Gly 25	GIZ	ato Ile	gca Ala	a tta	ggt Gly 30	AIC	acg Thr	96
cg Ar	t at g Il	t ati	е Туі	ccc Pro	gct Ala	gat Asp	gct Ala	a Lys	a caç Glr	g act Thr	gc Ala	g gta a Val	TITE	g att	aga e Arg	144
aa As	t ag n Se 5	r Hi	t aco	c aat	gaq n Glu	g cgo a Aro	y Phe	t cto	g gto ı Val	c aat L Asr	tc Se: 6	r III	g att	gaa e Gl	a aac u Asn	192
Se	c ag r Se	c gg r Gl	t gta y Va	a aaa l Ly:	a gaa s Gla	ı Lys	tc Se	a tto r Phe	c ato	c atte	- ru	a cco	g cca o Pro	a ct o Le	g ttt u Phe 80	240
gt Va	t ag	t ga r Gl	a cc u Pr	c aa o Ly	a ag s Se	c gaa r Gl	a aa u As	t ac n Th	t tt	g cg u Ar	t at g Il	t at	t ta e Ty	c ac r Th	c ggt r Gly	288

85		90	95	
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acg atc cct tcg gta Thr Ile Pro Ser Val 115	gat aaa aat Asp Lys Asn 120	gca ttg aac (Ala Leu Asn (ggc agg aat gtt Gly Arg Asn Val 125	ttg 384 Leu
caa ctg gcg att tta Gln Leu Ala Ile Leu 130	tcg cgc atg Ser Arg Met 135	Lys Leu Phe	ctc cgt cca att Leu Arg Pro Ile 140	caa 432 Gln
tta caa gaa tta ccc Leu Gln Glu Leu Pro 145	gca gaa gcg Ala Glu Ala 150	ccg gac aca (Pro Asp Thr 1	ctc aag ttt tcg Leu Lys Phe Ser	cga 480 Arg 160
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ctg gtt aac tta caa Leu Val Asn Leu Glr 180	ı gtg ggc agc ı Val Gly Ser	caa aag ttg (Gln Lys Leu (185	ggg aat gct atg Gly Asn Ala Met 190	gct 576 Ala
gca ccc aga gtt aat Ala Pro Arg Val Asi 195	tca caa att Ser Gln Ile 200	Pro Leu Pro	tca gga gtg cag Ser Gly Val Gln 205	gga 624 Gly
aag ctg aaa ttt cac Lys Leu Lys Phe Gli 210	g acc gtt aat n Thr Val Asn 215	Asp Tyr Gly	tca gta act ccg Ser Val Thr Pro 220	gtc 672 Val
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gcg Ala 65	ggc Gly	gtg Val	tat Tyr	cgg Arg	gtg Val 70	gat Asp	ctc Leu	tgg Trp	cgt Arg	aat Asn 75	gat Asp	gag Glu	ttc Phe	att Ile	ggt Gly 80		240
tcg Ser	cag Gln	gat Asp	atc Ile	gta Val 85	ttt Phe	gaa Glu	tcg Ser	aca Thr	aca Thr 90	gaa Glu	aat Asn	aca Thr	ggt Gly	gat Asp 95	aaa Lys		288
tca Ser	ggt Gly	ggg Gly	tta Leu 100	atg Met	ccc Pro	tgt Cys	ttt Phe	aac Asn 105	cag Gln	gta Val	ctt Leu	ctt Leu	gaa Glu 110	cga Arg	att Ile		336
ggc Gly	ctt Leu	aat Asn 115	agc Ser	agt Ser	gca Ala	ttt Phe	ccc Pro 120	gag Glu	tta Leu	gcc Ala	cag Gln	cag Gln 125	caa Gln	aac Asn	aat Asn		384
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gat Asp 145	ttt Phe	gca Ala	gcg Ala	atg Met	cgc Arg 150	ctg Leu	aac Asn	atc Ile	act Thr	att Ile 155	cct Pro	cag Gln	ata Ile	gcg Ala	ttg Leu 160		480
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ggt Gly	aac Asn	gat Asp 195	agc Ser	tat Tyr	ttt Phe	ttt Phe	agt Ser 200	gag Glu	ctc Leu	agc Ser	ggg Gly	att Ile 205	aat Asn	att Ile	ggc Gly		624
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gcc Ala	att Ile	att Ile	ccg Pro	ctg Leu 245	aaa Lys	agt Ser	gaa Glu	ctg Leu	gta Val 250	Met	gga Gly	gac Asp	ggc Gly	aat Asn 255	aca Thr	:	768
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gac Asp	gag Glu	cgc Arg	gat Asp 340	ggc Gly	aat Asn	cag Gln	cag Gln	aat Asn 345	tac Tyr	aca Thr	att Ile	ccg Pro	tat Tyr 350	tca Ser	aca Thr	1056
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					gcc Ala											1248
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					gac Asp											1344
					tcg Ser											1392
					tcg Ser 470											1440
gcg Ala	tat Tyr	cgt Arg	cga Arg	atg Met 485	gag Glu	ggg Gly	tac Tyr	gaa Glu	tat Tyr 490	gat Asp	tac Tyr	gac Asp	ggt Gly	gag Glu 495	cat His	1488
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tca Ser 545	gat Asp	acg Thr	tgg Trp	tat Tyr	cag Gln 550	gtg Val	ggg Gly	tat Tyr	acc Thr	agc Ser 555	Ser	tgg Trp	gtt Val	ggc Gly	atc Ile 560	1680
agt Ser	tat Tyr	tcg Ser	ctc Leu	tca Ser 565	ttt Phe	tcg Ser	tgg Trp	aat Asn	gaa Glu 570	tct Ser	gta Val	Gly	atc Ile	ccc Pro 575	gat Asp	1728
aac Asn	gaa Glu	cgt Arg	att Ile 580	gtc Val	gga Gly	ctt Leu	aat Asn	gtt Val 585	tca Ser	gtg Val	cct Pro	ttc Phe	aat Asn 590	gtt Val	ttg Leu	1776
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tcc Ser	ttt Phe 610	aac Asn	gcc Ala	aac Asn	cgt Arg	aac Asn 615	agc Ser	aac Asn	Gly	caa Gln	aat Asn 620	agc Ser	tgg Trp	ctg Leu	gca Ala	1872
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cat His	gaa Glu 690	aat Asn	ggc Gly	ata Ile	acg Thr	ctg Leu 695	agc Ser	cag Gln	cct Pro	tta Leu	ggg Gly 700	gat Asp	acc Thr	aat Asn	gtt Val	2112
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ggc Gly	att Ile	tta Leu	acc Thr	gac Asp 725	tgg Trp	cgc Arg	ggc Gly	tat Tyr	gcg Ala 730	gtg Val	atg Met	ctg Leu	tat Tyr	gcc Ala 735	acg Thr	2208
gtt Val	tat Tyr	cgg Arg	tat Tyr 740	aac Asn	cgt Arg	atc Ile	gcg Ala	ctt Leu 745	gat Asp	acc Thr	aat Asn	acg Thr	atg Met 750	ggg Gly	aat Asn	2256
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att acc gtt Ile Thr Val 785										2400
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gtt tat tta Val Tyr Leu	agt ggt Ser Gly 820	gcg cca Ala Pro	Leu S	tct ggt Ser Gly 825	gaa tt Glu Le	a ctg u Leu	gtt Val 830	cag Gln	tgg Trp	2496
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caa agc tta Gln Ser Leu 850	cag caa Gln Gln	gcc gtc Ala Val 855	act g Thr V	gtt att Val Ile	tcg gc Ser Al 86	a Val	tgc Cys	aca Thr	cat His	2592
cct ggc tca Pro Gly Ser 865	taa *									2604
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	atc Ile															288
	atg Met															336
	tat Tyr			_			_			_	_					384
	ggg Gly 130															432
	ttt Phe															480
	gtg Val															528
att Ile	agt Ser	ttt Phe	ggt Gly 180	ggc Gly	cgg Arg	gtt Val	gaa Glu	gta Val 185	ccg Pro	caa Gln	aac Àsn	tgc Cys	gaa Glu 190	tta Leu	aat Asn	576
	ggg Gly															624
	agt Ser 210															672
	aag Lys															720
	aca Thr															768
	gac Asp															816
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ggt Gly	aac Asn	gtt Val 35	gtt Val	gat Asp	ttc Phe	tcc Ser	tgt Cys 40	acc Thr	gta Val	aac Asn	aca Thr	gcg Ala 45	gat Asp	att Ile	gat Asp	144
aag Lys	acg Thr 50	gta Val	gat Asp	tta Leu	ggc Gly	aga Arg 55	tgg Trp	cct Pro	acg Thr	aca Thr	caa Gln 60	cta Leu	ctg Leu	aac Asn	gct Ala	192
ggc Gly 65	gat Asp	acc Thr	acg Thr	gca Ala	ctc Leu 70	gtc Val	cct Pro	ttt Phe	agc Ser	ctg Leu 75	cgg Arg	ctg Leu	gag Glu	gga Gly	tgt Cys 80	240
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acc Thr	aac Asn	ctg Leu	ctg Leu 100	gct Ala	ctg Leu	gat Asp	gat Asp	ccc Pro 105	gca Ala	atg Met	gca Ala	caa Gln	acc Thr 110	gtc Val	gcc Ala	336
atc Ile	gaa Glu	tta Leu 115	cgt Arg	aat Asn	agc Ser	gat Asp	cgc Arg 120	tcc Ser	cgg Arg	ctc Leu	gca Ala	ctg Leu 125	ggg Gly	gag Glu	gcg Ala	384
	ccg Pro 130															432
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-118-

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cga d Arg I	ctg Leu	gtc Val	gtg Val 20	cgt Arg	ctg Leu	gtg Val	cat His	gat Asp 25	cgt Arg	gat Asp	gcc Ala	tgg Trp	cgt Arg 30	ctt Leu	gcg Ala		96
gat t Asp 1	tat Tyr	tac Tyr 35	gca Ala	gag Glu	aat Asn	cgc Arg	cat His 40	ttc Phe	ctc Leu	aag Lys	ccc Pro	tgg Trp 45	gag Glu	cca Pro	gtg Val		144
cgc q	gac Asp 50	gaa Glu	agc Ser	cac His	tgt Cys	tat Tyr 55	cca Pro	tca Ser	ggc Gly	tgg Trp	cag Gln 60	gcc Ala	agg Arg	ctg Leu	ggg ggg		192
atg a Met 1	att Ile	aac Asn	gaa Glu	ttt Phe	cat His 70	aaa Lys	caa Gln	ggt Gly	tca Ser	gct Ala 75	ttc Phe	tac Tyr	ttt Phe	ggc Gly	tta Leu 80		240
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ctg Leu	gaa Glu	aag Lys	cag Gln 20	gtg Val	acc Thr	acg Thr	ccg Pro	gag Glu 25	caa Gln	tac Tyr	ccg Pro	ctc Leu	tca Ser 30	gtc Val	aat Asn		96
ggt Gly	gta Val	gtc Val 35	acg Thr	gcc Ala	tgt Cys	aat Asn	cag Gln 40	a a a Lys	acg Thr	aac Asn	cgt Arg	gaa Glu 45	ccg Pro	gtc Val	atg Met	1	L44
						gtg Val 55										3	192
cgt Arg 65	cat His	tat Tyr	cta Leu	cgc Arg	aca Thr 70	gtg Val	agc Ser	ggt Gly	ttt Phe	ggt Gly 75	aat Asn	cgg Arg	gtc Val	acc Thr	aaa Lys 80	2	240
						aat Asn										2	288
						atc Ile										3	336
						agc Ser										3	384
gat Asp	atg Met 130	gcg Ala	gaa Glu	gtg Val	gag Glu	tcg Ser 135	acg Thr	ctg Leu	gaa Glu	caa Gln	ctg Leu 140	gca Ala	aat Asn	cgc Arg	gaa Glu	4	132
gat Asp 145	ggt Gly	cct Pro	ttt Phe	gtg Val	gtg Val 150	cgt Arg	ctg Leu	gcc Ala	cgc Arg	gaa Glu 155	ccg Pro	ggt Gly	aaa Lys	cgc Arg	gaa Glu 160	4	180
						ttc Phe										ţ	528
						gcg Ala											576

gaa gcc ctg g Glu Ala Leu G 195	gaa atc gaa (Glu Ile Glu V	gtg gca gaa Val Ala Glu 200	a ctg aaa (u Leu Lys (cag cgt ctt Gln Arg Leu 205	gat tcg Asp Ser	624
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gca gaa aat Ala Glu Asn	ctg cgc gat Leu Arg Asp 100	Ala Glu A	gg ctg gtg rg Leu Val 05	gaa ctg gcg Glu Leu Ala 110	Ala Arg	336
aaa aaa ctg Lys Lys Leu 115	acg ttg atg Thr Leu Met	gtc ggt to Val Gly Pl 120	tt aac cgt he Asn Arg	cgt ttc gca Arg Phe Ala 125	cca ctc Pro Leu	384
tac ggt gag Tyr Gly Glu 130	tta aaa acg Leu Lys Thr	caa ctc go Gln Leu A 135	cc acc gca la Thr Ala	gcc tcg cta Ala Ser Leu 140	aga atg Arg Met	432
gat aaa cat Asp Lys His 145	cgt agc aat Arg Ser Asn 150	Ser Val G	gg cca cac Sly Pro His 155	gat ctt tat Asp Leu Tyr	ttc acg Phe Thr 160	480

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cag Gln 225	gcc Ala	gtg Val	act Thr	gac Asp	ggt Gly 230	gcg Ala	ctc Leu	atc Ile	gac Asp	att Ile 235	acg Thr	gat Asp	atg Met	cgc Arg	gaa Glu 240	720
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cto	tto Lev	act Thr	gtg Val	Leu	ggc	cto Leu	gat Asp	cgc Arg 25	Trp	atg Met	ago Ser	tgg Trp	aaa Lys 30	Thr	gcg Ala	96
cct	: tat	ato	tac	gac	gaa	ttg	caç	gat	cto	ccc	tac	: cgc	: caç	gto	ggt	144

Pro	Tyr	Ile 35	Tyr	Asp	Glu	Leu	Gln 40	Asp	Leu	Pro	Tyr	Arg 45	Gln	Val	Gly	
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cca Pro	tca Ser	gat Asp 115	att Ile	gtt Val	ctc Leu	gat Asp	tac Tyr 120	gca Ala	ggc Gly	ttt Phe	cgt Arg	acg Thr 125	ctg Leu	gat Asp	tcc Ser	384
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gto Val 225	Thr	ccc Pro	gaa Glu	cag Gln	tta Leu 230	Leu	gaa Glu	tta Leu	caa Gln	aag Lys 235	Lys	caa Gln	gga Gly	aag Lys	tag : *	720
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gat aaa cgg Asp Lys Arg 35	gtt aaa Val Lys	aat gca Asn Ala	ccg Pro 40	gaa Glu	ccg Pro	gtg Val	tat Tyr	gtc Val 45	tgg Trp	cga Arg	gca Ala	144
aaa aat ccc Lys Asn Pro 50	gga ctc Gly Leu	ttt ttc Phe Phe 55	Ala	tat Tyr	atg Met	gtg Val	gca Ala 60	tat Tyr	atc Ile	ggc Gly	ttc Phe	192
gga att tta Gly Ile Leu 65	tct atc Ser Ile	ggc atg Gly Met 70	att Ile	gtt Val	tat Tyr	ctt Leu 75	att Ile	ttc Phe	tat Tyr	cgt Arg	taa *	240
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att Ile	acc Thr	atg Met 115	caa Gln	gcg Ala	ctg Leu	gtg Val	atg Met 120	gct Ala	cat His	gcc Ala	tgc Cys	tat Tyr 125	ggg Gly	cat His	aac Asn		384
tct Ser	ttc Phe 130	ttc Phe	aaa Lys	aac Asn	aat Asn	tac Tyr 135	tta Leu	ttc Phe	cgt Arg	agc Ser	tgg Trp 140	acc Thr	gac Asp	gcc Ala	agt Ser		432
tcg Ser 145	att Ile	gtc Val	gat Asp	tat Tyr	ctg Leu 150	att Ile	ttt Phe	gcc Ala	cgt Arg	aaa Lys 155	tat Tyr	att Ile	acc Thr	gag Glu	tgc Cys 160		480
gaa Glu	gag Glu	cgt Arg	tat Tyr	ggc Gly 165	gtt Val	gat Asp	gaa Glu	gta Val	gaa Glu 170	cgg Arg	ctt Leu	ctg Leu	gac Asp	tcg Ser 175	tgc Cys		528
cac His	gcg Ala	ctg Leu	atg Met 180	aac Asn	tac Tyr	ggc Gly	gtg Val	gac Asp 185	cgg Arg	tac Tyr	aaa Lys	cgc Arg	ccg Pro 190	caa Gln	aaa Lys		576
atc Ile	tcg Ser	ctg Leu 195	caa Gln	gaa Glu	gag Glu	aaa Lys	gcc Ala 200	cgg Arg	cag Gln	aaa Lys	agt Ser	cgc Arg 205	gaa Glu	gag Glu	tat Tyr		624
					aat Asn												672
gaa Glu 225	gag Glu	aaa Lys	acg Thr	gtt Val	gct Ala 230	gaa Glu	gcg Ala	cgc Arg	cgc Arg	tat Tyr 235	ccg Pro	tcc Ser	gaa Glu	cca Pro	caa Gln 240		720
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					act Thr												864
					ctt Leu												912
gaa Glu 305	cgt Arg	ttt Phe	atg Met	ctg Leu	gag Glu 310	ttt Phe	ttg Leu	cac His	agc Ser	cac His 315	acc Thr	aat Asn	gtg Val	gtc Val	ttc Phe 320		960
cag Gln	ccc Pro	ccc Pro	tat Tyr	aac Asn 325	agc Ser	ccg Pro	tgg Trp	tac Tyr	agc Ser 330	ggc Gly	atc	aac Asn	ccg Pro	tat Tyr 335	gcc Ala		1008
ctc Leu	ggg	ttc Phe	gcc Ala 340	atg Met	ttc Phe	cag Gln	gat Asp	att Ile 345	aaa Lys	cgg Arg	att Ile	tgt Cys	cag Gln 350	tcg Ser	cca Pro	9	1056

acg Thr	gaa Glu	gaa Glu 355	gac Asp	aaa Lys	tac Tyr	tgg Trp	ttc Phe 360	ccg Pro	gat Asp	atc Ile	gcc Ala	ggt Gly 365	tcc Ser	gac Asp	tgg Trp	1104
ctg Leu	gaa Glu 370	acg Thr	ctg Leu	cat His	ttc Phe	gcg Ala 375	atg Met	cgt Arg	gat Asp	ttc Phe	aaa Lys 380	gat Asp	gag Glu	agt Ser	ttt Phe	1152
atc Ile 385	agc Ser	cag Gln	ttc Phe	ctg Leu	tca Ser 390	ccg Pro	aaa Lys	gtg Val	atg Met	cgt Arg 395	gat Asp	ttc Phe	cgc Arg	ttc Phe	ttc Phe 400	1200
acc Thr	gtg Val	ctg Leu	gat Asp	gac Asp 405	gat Asp	cgg Arg	cat His	aat Asn	tat Tyr 410	ctg Leu	gag Glu	att Ile	tcc Ser	gct Ala 415	att Ile	1248
cat His	aat Asn	gaa Glu	gaa Glu 420	ggt Gly	tat Tyr	cgg Arg	gag Glu	atc Ile 425	cgt Arg	aac Asn	cgg Arg	tta Leu	tcg Ser 430	tcg Ser	caa Gln	1296
tat Tyr	aac Asn	tta Leu 435	agt Ser	aat Asn	ctg Leu	gag Glu	ccg Pro 440	aat Asn	att Ile	cag Gln	atc Ile	tgg Trp 445	aac Asn	gtg Val	gat Asp	1344
ttg Leu	cgc Arg 450	ggc Gly	gac Asp	cgt Arg	tcg Ser	ctg Leu 455	acg Thr	ctg Leu	cgt Arg	tat Tyr	att Ile 460	cca Pro	cat His	aat Asn	cgc Arg	1392
gca Ala 465	Pro	ctg Leu	gat Asp	cgg Arg	ggg Gly 470	cgc Arg	aaa Lys	gaa Glu	gtc Val	ctg Leu 475	aag Lys	cat His	gtg Val	cat His	cgc Arg 480	1440
ctg Leu	tgg Trp	gga Gly	ttt Phe	gat Asp 485	gtg Val	atg Met	ctc Leu	gaa Glu	cag Gln 490	caa Gln	aac Asn	gaa Glu	gac Asp	ggc Gly 495	agc Ser	1488
atc Ile	gag Glu	ttg Leu	ctg Leu 500	gaa Glu	cgt Arg	tgc Cys	ccg Pro	cca Pro 505	Arg	atg Met	gga Gly	aat Asn	ctg Leu 510	taa *		1533
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cta Leu	ctg Lev	tct Ser	gtt Val 20	Ala	ggc Gly	gcc	gga Gly	att Ile 25	Val	tgg Trp	act Thr	ctc	tat Tyr 30	Asn	ggc Gly	96

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aca Thr	gcg Ala 50	cag Gln	atc Ile	aag Lys	cag Gln	ttg Leu 55	tta Leu	att Ile	gat Asp	ggg Gly	Val	aat Asn	cca Pro	gat Asp	acg Thr		192
tta Leu 65	cct Pro	gtg Val	tac Tyr	ttt Phe	aac Asn 70	cgg Arg	atg Met	atg Met	gat Asp	gtt Val 75	agt Ser	cag Gln	gat Asp	atc Ile	ttg Leu 80		240
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agt Ser	gat Asp	ggc Gly	atg Met 100	tta Leu	aat Asn	aac Asn	ata Ile	cct Pro 105	gct Ala	agt Ser	gag Glu	aca Thr	atc Ile 110	agc Ser	gca Ala		336
gct Ala	ggc Gly	att Ile 115	tac Tyr	aga Arg	agc Ser	Ile	att Ile 120	aat Asn	gat Asp	aca Thr	gag Glu	ata Ile 125	gat Asp	gct Ala	tta Leu		384
cga Arg	att Ile 130	aat Asn	att Ile	gat Asp	gaa Glu	gtt Val 135	tcg Ser	cca Pro	tca Ser	tta Leu	acg Thr 140	gtt Val	act Thr	gtg Val	gct Ala		432
aaa Lys 145	ttg Leu	gct Ala	tca Ser	gcc Ala	aga Arg 150	cat His	aac Asn	atg Met	ctt Leu	gaa Glu 155	cag Gln	tat Tyr	aaa Lys	att Ile	aat Asn 160	·	480
agc Ser	att Ile	ata Ile	att Ile	tgc Cys 165	att Ile	gtc Val	gcc Ala	att Ile	gta Val 170	ctt Leu	tgc Cys	tca Ser	gta Val	tta Leu 175	agt Ser		528
ccg Pro	ctg Leu	tta Leu	atc Ile 180	aga Arg	acg Thr	gga Gly	tta Leu	cga Arg 185	gag Glu	atc Ile	aaa Lys	aag Lys	ttg Leu 190	agt Ser	ggt Gly		576
gta Val	acg Thr	gaa Glu 195	gcg Ala	ctg Leu	aat Asn	tat Tyr	aac Asn 200	gat Asp	agc Ser	cga Arg	gag Glu	cct Pro 205	gtt Val	gag Glu	gtt Val		624
agc Ser	gca Ala 210	tta Leu	ccg Pro	aga Arg	gaa Glu	cta Leu 215	aaa Lys	cct Pro	ctt Leu	ggg Gly	cag Gln 220	Ala	ttg Leu	aat Asn	aaa Lys		672
atg Met 225	cat His	cat His	gct Ala	tta Leu	gtc Val 230	aaa Lys	gat Asp	ttt Phe	gag Glu	cgt Arg 235	cta Leu	agt Ser	cag Gln	ttt Phe	gct Ala 240		720
gac Asp	gat Asp	ctc Leu	gct Ala	cat His 245	gaa Glu	ctt Leu	aga Arg	acg Thr	cca Pro 250	att Ile	aat Asn	gca Ala	tta Leu	ctg Leu 255	ggt Gly		768
cag Gln	aat Asn	cag Gln	gtt Val 260	Thr	ctc Leu	agt Ser	caa Gln	acc Thr 265	Arg	agt Ser	atc Ile	gct Ala	gaa Glu 270	Tyr	caa Gln		816 .

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					ttt Phe											912
gtg Val 305	aaa Lys	ctg Leu	gac Asp	tcg Ser	ctt Leu 310	tct Ser	ctc Leu	aat Asn	aag Lys	gaa Glu 315	gtc Val	gaa Glu	aat Asn	ttg Leu	ttg Leu 320	960
gac Asp	tat Tyr	ctt Leu	gaa Glu	tac Tyr 325	ctt Leu	tca Ser	gac Asp	gag Glu	aaa Lys 330	gag Glu	att Ile	tgc Cys	ttt Phe	aag Lys 335	gtc Val	1008
					atc Ile											1056
					gtt Val											1104
cgt Arg	att Ile 370	cat His	ata Ile	acc Thr	agt Ser	ttt Phe 375	ctt Leu	gat Asp	acc Thr	aac Asn	agc Ser 380	tat Tyr	ctt Leu	aat Asn	att Ile	1152
					gga Gly 390											1200
cgt Arg	aga Arg	ttt Phe	tgg Trp	cgg Arg 405	gga Gly	gat Asp	aat Asn	tcg Ser	cgt Arg 410	cat His	tcc Ser	gta Val	ggt Gly	cag Gln 415	gga Gly	1248
cta Leu	ggc Gly	ctt Leu	tct Ser 420	tta Leu	gtc Val	aaa Lys	gcg Ala	att Ile 425	gcc Ala	gaa Glu	ttg Leu	cat His	999 Gly 430	gga Gly	agt Ser	1296
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-		•	aat Asn													1359
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Met 1	Asn	Gln	Ala	Val 5	Ser	Ile	Thr	Tyr	Asp 10	Leu	Trp	His	Ile	Ile 15	Phe	
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acg Thr	cag Gln	ggg Gly 35	ctt Leu	tcc Ser	gaa Glu	gcg Ala	ggt Gly 40	tat Tyr	gtc Val	atc Ile	gat Asp	gcc Ala 45	Val	tct Ser	gat Asp	144
ggc Gly	aga Arg 50	gat Asp	ggg Gly	ctt Leu	tat Tyr	ctt Leu 55	gcg Ala	ctg Leu	aag Lys	gat Asp	gat Asp 60	tat Tyr	gca Ala	ttg Leu	atc Ile	192
att Ile 65	ctg Leu	gat Asp	att Ile	atg Met	ctt Leu 70	ccg Pro	ggt Gly	atg Met	gat Asp	ggc Gly 75	tgg Trp	cag Gln	atc Ile	tta Leu	caa Gln 80	240
acg Thr	tta Leu	aga Arg	aca Thr	gca Ala 85	aag Lys	caa Gln	acc Thr	cct Pro	gtt Val 90	att Ile	tgc Cys	ctt Leu	act Thr	gca Ala 95	agg Arg	288
gat Asp	tct Ser	gtc Val	gat Asp 100	gac Asp	aga Arg	gtc Val	aga Arg	ggg Gly 105	ctg Leu	gac Asp	agt Ser	ggg Gly	gca Ala 110	aat Asn	gat Asp	336
tat Tyr	ctg Leu	gta Val 115	aaa Lys	cct Pro	ttt Phe	tca Ser	ttt Phe 120	tct Ser	gag Glu	ttg Leu	ctg Leu	gca Ala 125	agg Arg	gtt Val	cgg Arg	384
gca Ala	caa Gln 130	tta Leu	agg Arg	caa Gln	cat His	cac His 135	gct Ala	ttg Leu	aat Asn	tca Ser	aca Thr 140	tta Leu	gaa Glu	atc Ile	agc Ser	432
ggc Gly 145	tta Leu	aga Arg	atg Met	gac Asp	tct Ser 150	gtt Val	agt Ser	cat His	agt Ser	gtg Val 155	agc Ser	agg Arg	gac Asp	aat Asn	atc Ile 160	480
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tcc Ser	aga Arg	gct Ala	ggc Gly 180	gaa Glu	att Ile	ata Ile	ccc Pro	aga Arg 185	acg Thr	gtt Val	att Ile	gcg Ala	agt Ser 190	gaa Glu	att Ile	576
tgg Trp	gga Gly	atc Ile 195	aac Asn	ttt Phe	gat Asp	agt Ser	gat Asp 200	Thr	aat Asn	acg Thr	gtg Val	gac Asp 205	Val	gcc Ala	att Ile	624
cgc Arg	agg Arg 210	Leu	cgc Arg	gca Ala	aaa Lys	gtt Val 215	Asp	gat Asp	cct Pro	ttt Phe	cct Pro 220	gaa Glu	aag Lys	cta Leu	att Ile	672
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act aac aaa ata tcg ctt gtc agt tat att gta tgg cag gaa aga tat Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg Tyr 35 40 45	144
gcg act gat att aca gat ccc caa agt gga gag ttt atg acc att aaa Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile Lys 50 . 55 60	192
aat aag atg ttg ctg ggt gcg ctt ttg ctg gtt acc agt gcc gcc tgg Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala Trp 65 70 75 80	240
gcc gca cca gcc acc gcg ggt tcg acc aat acc tcg gga att tct aag Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser Lys 85 90 95	288
tat gag tta agt agt ttc att gct gac ttt aag cat ttc aaa cca ggg Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro Gly 100 105 110	336
gac acc gta cca gaa atg tac cgt acc gat gag tac aac att aag cag Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys Gln 115 120 125	384
tgg cag ttg cgt aac ctg ccc gcg cct gat gcc ggg acg cac tgg acc Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp Thr 130 135 140	432
tat atg ggt ggc gcg tac gtg ttg atc agc gac acc gac ggt aaa atc Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys Ile 145 150 155	480
att aaa gcc tac gac ggt gag att ttt tat cat cgc taa Ile Lys Ala Tyr Asp Gly Glu Ile Phe Tyr His Arg * 165 170	519

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atc Ile	ccc Pro	agc Ser	gcc Ala 20	atc Ile	tta Leu	ctt Leu	ggt Gly	gcg Ala 25	ctt Leu	cat His	ggc Gly	ctg Leu	gaa Glu 30	cca Pro	G1A aaa		96
cac His	tca Ser	aaa Lys 35	acg Thr	atg Met	atg Met	gcg Ala	gcg Ala 40	ttt Phe	atc Ile	atc Ile	gcc Ala	atc Ile 45	aaa Lys	ggc Gly	acc Thr		144
att Ile	aaa Lys 50	caa Gln	gcg Ala	gtg Val	atg Met	ctc Leu 55	gga Gly	ctg Leu	gca Ala	gca Ala	act Thr 60	att Ile	tcg Ser	cat His	acc Thr		192
gca Ala 65	gtg Val	gtc Val	tgg Trp	tta Leu	att Ile 70	gcc Ala	ttt Phe	ggc Gly	ggg Gly	atg Met 75	gtg Val	atc Ile	agc Ser	aag Lys	cgc Arg 80		240
ttt Phe	act Thr	gct Ala	caa Gln	tca Ser 85	gca Ala	gaa Glu	ccg Pro	tgg Trp	ctc Leu 90	cag Gln	ctg Leu	att Ile	tcc Ser	gca Ala 95	gtg Val		288
atc Ile	att Ile	att Ile	agc Ser 100	acc Thr	gcg Ala	ttc Phe	tgg Trp	atg Met 105	ttc Phe	tgg Trp	cgt Arg	acc Thr	tgg Trp 110	cgc Arg	ggc Gly		336
gaa Glu	cgc Arg	aac Asn 115	tgg Trp	ctg Leu	gag Glu	aat Asn	atg Met 120	cac His	ggg Gly	cat His	gat Asp	tat Tyr 125	gag Glu	cat His	cat His		384
cat His	cac His 130	Asp	cac His	gaa Glu	cat His	cac His 135	cac His	gac Asp	cat His	gga Gly	cat His 140	cat His	cac His	cat His	cac His		432
gaa Glu 145	His	Gly	Glu	Tyr	Gln	gat Asp	Ala	His	Ala	Arg	Ala	cat His	gcc Ala	aat Asn	gac Asp 160		480
att Ile	aaa Lys	cga Arg	cgc Arg	ttt Phe 165	Asp	ggt Gly	aga Arg	gag Glu	gtc Val 170	acc Thr	aac Asn	tgg Trp	caa Gln	att Ile 175	ttg Leu		528
tta Leu	ttt Phe	ggc Gly	tta Leu 180	acc Thr	ggt Gly	ggc	ctt Leu	atc Ile 185	Pro	tgc Cys	ccg Pro	gca Ala	gca Ala 190	att Ile	acc Thr		576
gtg Val	ctg Leu	ttg Leu 195	Ile	tgc Cys	att	cag Gln	ttg Leu 200	Lys	gcc Ala	ctg Leu	aca Thr	ctg Leu 205	Gly	gca Ala	aca Thr	•	624
ctg Leu	gtc Val 210	Val	agt Ser	ttc Phe	agc Ser	att Ile 215	Gly	ctg Leu	gcg Ala	tta Leu	acg Thr 220	Leu	gtc Val	acc Thr	gta Val		672

ggc gtt ggc gca gca atc agc gtt cag cag gtc gca aaa cgc tgg agc Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser 235 240	720
gga ttt aac act ctc gct aaa cgc gcc ccc tat ttt tcc agt ctg ttg Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu 245 250 255	768
att ggc tta gtc ggt gtg tat atg ggc gta cat ggc ttc atg ggc ata Ile Gly Leu Val Gly Val Tyr Met Gly Val His Gly Phe Met Gly Ile 260 265 270	816
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atc gcc ctg att tgt gaa ggt aac cct gcc gat cta ctg ggc cag tgg Ile Ala Leu Ile Cys Glu Gly Asn Pro Ala Asp Leu Leu Gly Gln Trp 35 40 45	144
gtg ctg gta cac gtc gga ttt gcc atg agc atc atc gac gaa gat gaa Val Leu Val His Val Gly Phe Ala Met Ser Ile Ile Asp Glu Asp Glu 50 55 60	192
gcc aaa gcc aca tta gac gca ctg cgc caa atg gat tac gac att acc Ala Lys Ala Thr Leu Asp Ala Leu Arg Gln Met Asp Tyr Asp Ile Thr 65 70 75 80	240
agc gcg tga Ser Ala *	249
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-132-

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art o	50					55					60					
Val I 65					_	_		ctc Leu		•	_	-			-	240
gaa a Glu L																288
ggc g Gly G	gaa Slu	ctg Leu	gac Asp 100	ggt Gly	gtt Val	tcg Ser	caa Gln	tat Tyr 105	ctc Leu	tcc Ser	tgt Cys	tcg Ser	ctg Leu 110	atg Met	tcg Ser	336
ccg c																384
gac t Asp C	gc Cys 130	gca Ala	cga Arg	atg Met	atc Ile	ctt Leu 135	tcg Ser	ctg Leu	cca Pro	gtc Val	acg Thr 140	aat Asn	ccg Pro	gat Asp	gta Val	432
cca c Pro H 145																480
aat g Asn A	-	tga *														489
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Glu	gtt Val	ccg Pro	gcg Ala	ttg Leu 85	ttt Phe	acc Thr	aac Asn	aaa Lys	atc Ile 90	tct Ser	ccg Pro	cat His	cag Gln	ctt Leu 95	ggc Gly	288
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, aag Lys	ctg Leu	acc Thr 115	ctg Leu	gtc Val	ggc Gly	gtg Val	atc Ile 120	ccg Pro	gaa Glu	tcg Ser	ctg Leu	gag Glu 125	cca Pro	cac His	atc Ile	384
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gcg Ala	ctg Leu	gac Asp 115	tgg Trp	gtg Val	gac Asp	atc Ile	act Thr 120	tct Ser	gca Ala	ctg Leu	caa Gln	gct Ala 125	gac Asp	cca Pro	acc Thr	3	84
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gaa Glu	tac Tyr	ctg Leu	atc Ile	aaa Lys 325	Gly	att Ile	cag Gln	gaa Glu	agc Ser 330	Ala	aag Lys	cac His	tcc Ser	tgg Trp 335	tat Tyr	1	800

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gat Asp	ccg Pro 530	Asn	aaa Lys	ccg Pro	ctg Leu	gaa Glu 535	Val	gtg Val	g cgt . Arg	Thr	Ile 540	: His	tcc Ser	ttt Phe	gac Asp	1632
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aag cgt ctg gtg ttc ggt ctg ggc tct gtc tct gac ctg aac ggc ggc Lys Arg Leu Val Phe Gly Leu Gly Ser Val Ser Asp Leu Asn Gly Gly 35 40 45	144
ttc ccg tgg ggc gtg tgg atc gcg ttt gac ctg ctg att ggc acc ggc Phe Pro Trp Gly Val Trp Ile Ala Phe Asp Leu Leu Ile Gly Thr Gly 50 55 60	
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cgt ggg caa tac cat ccg ctg gtg cgt ccg gcg ctg ttg gcg agt ctg Arg Gly Gln Tyr His Pro Leu Val Arg Pro Ala Leu Leu Ala Ser Leu 85 90 95	
ttt ggt tac tca ctg ggt ggc ttg tcg atc act atc gac gtg ggt cgc Phe Gly Tyr Ser Leu Gly Gly Leu Ser Ile Thr Ile Asp Val Gly Arg 100 105 110	: 336 I
tac tgg aac ctg ccg tac ttc tac att ccg ggt cac ttc aac gtg aac Tyr Trp Asn Leu Pro Tyr Phe Tyr Ile Pro Gly His Phe Asn Val Asr 115 120 125	
tcg gta ctg ttc gag acg gcg gtc tgt atg acc atc tat atc ggc gtc Ser Val Leu Phe Glu Thr Ala Val Cys Met Thr Ile Tyr Ile Gly Val 130 135 140	
Met Ala Leu Glu Phe Ala Pro Ala Leu Phe Glu Arg Leu Gly Trp Lys	3
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ggt gcg ctg ctg ccg acc atg cac cag tct tca atg ggg tcg ctg atg Gly Ala Leu Leu Pro Thr Met His Gln Ser Ser Met Gly Ser Leu Met 180 185 190	576 :
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atg Met	cac His	tgc Cys 115	gtc Val	gat Asp	ccg Pro	aac Asn	tgt Cys 120	gtc Val	tct Ser	gtg Val	tgc Cys	ccg Pro 125	gtc Val	tct Ser	gca Ala	384
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tgc Cys	gta Val	gaa Glu 195	gtg Val	tgc Cys	ccg Pro	gcg Ala	ggc Gly 200	Ala	gtg Val	att Ile	ttc Phe	ggt Gly 205	acg Thr	cgt Arg	gaa Glu	624
gag Glu	ctg Leu 210	atg Met	gcg Ala	gag Glu	gcg Ala	aaa Lys 215	Lys	cgt Arg	ctg Leu	gcg Ala	ctg Leu 220	Lys	cct Pro	ggc Gly	agc Ser	672
gaa Glu	tac Tyr	cac His	tat Tyr	ccg Pro	cgt Arg	cag Gln	acg Thr	ctg Leu	aaa Lys	tct Ser	ggc Gly	gac Asp	act Thr	tac Tyr	ctg Leu	720

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Met Leu Gln Cys Gly 1 5 tcg tcg ttg ccc gtt Ser Ser Leu Pro Val 20 gat tgt gcg ccg cag	Ala Lys Asn Val Asn 10 gct gcc gtc tta cct Ala Ala Val Leu Pro	gaa tta ctt acc gct Glu Leu Leu Thr Ala 30 ccg acc ggg gcc ggg	ctc 96 Leu
Met Leu Gln Cys Gly 1 5 tcg tcg ttg ccc gtt Ser Ser Leu Pro Val 20 gat tgt gcg ccg cag Asp Cys Ala Pro Gln 35 tca acc tgg ctg ccg	Ala Lys Asn Val Asn 10 gct gcc gtc tta cct Ala Ala Val Leu Pro 25 gta tta tta agt gcg Val Leu Leu Ser Ala	Pro Leu Glu Arg Phe 15 gaa tta ctt acc gct Glu Leu Leu Thr Ala 30 ccg acc ggg gcc ggg Pro Thr Gly Ala Gly 45 cat ccc ggc att aacc	ctc 96 Leu 96 Lys 144 Lys 192
Met Leu Gln Cys Gly 1 5 tcg tcg ttg ccc gtt Ser Ser Leu Pro Val 20 gat tgt gcg ccg cag Asp Cys Ala Pro Gln 35 tca acc tgg ctg ccg Ser Thr Trp Leu Pro 50 aaa att atc ctg ctg	Ala Lys Asn Val Asn 10 gct gcc gtc tta cct Ala Ala Val Leu Pro 25 gta tta tta agt gcg Val Leu Leu Ser Ala 40 ctg caa ctg ctg gcg Leu Gln Leu Leu Ala	gaa tta ctt acc gct Glu Leu Leu Thr Ala 30 ccg acc ggg gcc ggg Pro Thr Gly Ala Gly 45 cat ccc ggc att aac His Pro Gly Ile Asn 60 gcg gcg cgt aac gtc	ctc 96 Leu 96 Leu 144 Lys 192 Gly 192 Gcg 240

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ctg Leu	agc Ser 130	ggt Gly	gtt Val	gga Gly	ctg Leu	gtg Val 135	atc Ile	ctt Leu	gat Asp	gaa Glu	ttt Phe 140	cat His	gag Glu	cgc Arg	agc Ser		432
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					ggc Gly												816
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caa Gln	agc Ser 370	gat Asp	ctt Leu	tcc Ser	ggt Gly	ttg Leu 375	ctg Leu	atg Met	gaa Glu	tta Leu	ctg Leu 380	caa Gln	tgg Trp	gga Gly	tgc Cys	1	152
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gaa Glu	cgg Arg	ctt Leu	agt Ser 420	gcg Ala	caa Gln	ggg Gly	caa Gln	aaa Lys 425	atg Met	gca Ala	gcg Ala	ctg Leu	ggt Gly 430	aac Asn	gat Asp	1.	296
ccg Pro	cgt Arg	tta Leu 435	gcg Ala	gca Ala	atg Met	ctg Leu	gtt Val 440	agc Ser	gcg Ala	aag Lys	aac Asn	gac Asp 445	gac Asp	gaa Glu	gct Ala	1	344
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cat His	tac Tyr	act Thr	gtg Val	ccg Pro 725	acg Thr	gga Gly	agc Ser	cgg Arg	atc Ile 730	gcc Ala	att Ile	cgt Arg	tat Tyr	cat His 735	gaa Glu	2208
gat Asp	aac Asn	ccg Pro	ccc Pro 740	gcg Ala	ctg Leu	gcg Ala	gtg Val	aga Arg 745	atg Met	caa Gln	gag Glu	·atg Met	ttt Phe 750	ggc Gly	gag Glu	2256
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gac Asp 785	ttc Phe	tgg Trp	aaa Lys	gga Gly	gcg Ala 790	tac Tyr	cgt Arg	gag Glu	gtg Val	caa Gln 795	aaa Lys	gag Glu	atg Met	aaa Lys	800 GTA GGB	2400
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cat cgt ggt ggt gaa His Arg Gly Gly Glu 35	atc tgg ttg g Ile Trp Leu G 40	ggt agt ctg gct gct Gly Ser Leu Ala Ala 45	ttg ctg gaa 144 Leu Leu Glu
ggg ctg gga ttt ggt Gly Leu Gly Phe Gly 50	gag cgt ttc g Glu Arg Phe V 55	gtg cgc acc gct ttg Val Arg Thr Ala Leu 60	ttt cgt ctt 192 Phe Arg Leu
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aaa att tat cgc gca Lys Ile Tyr Arg Ala 100	Glu Gln Pro F	gca tgg gat ggt aaa Ala Trp Asp Gly Lys 105	tgg ctc ctg 336 Trp Leu Leu 110
ttg ctc tcg gaa ggt Leu Leu Ser Glu Gly 115	tta gat aaa t Leu Asp Lys S 120	tca acg ctg gct gat Ser Thr Leu Ala Asp 125	gtc aaa aag 384 Val Lys Lys
cag ttg atc tgg caa Gln Leu Ile Trp Glr 130	n ggt ttt ggc o n Gly Phe Gly <i>I</i> 135	gca ctg gca ccc agc Ala Leu Ala Pro Ser 140	ctg atg gca 432 Leu Met Ala
tcg ccg tcg caa aaa Ser Pro Ser Gln Ly: 145	a ctg gcc gat o s Leu Ala Asp \ 150	gta cag aca ctt ttg Val Gln Thr Leu Leu 155	cat gaa gcg 480 His Glu Ala 160
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ctg gtg ccg ct Leu Val Pro Le 210	tt tta aaa eu Leu Lys	gag gcg Glu Ala 215	gca gac Ala Asp	gag tta Glu Leu 220	Thr P	eg gag co Glu	cgg Arg	672
gca ttt cat at Ala Phe His Il 225	tt cag ctt le Gln Leu 230	tta ctg Leu Leu	atc cat Ile His	ttt tat Phe Tyr 235	cgc cg	gt gtc rg Val	gtc Val 240	720
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gaa ctg cct go Glu Leu Pro Al 290	cg ccg gga la Pro Gly	agc ctg Ser Leu 295	tat ttt Tyr Phe	caa cgt Gln Arg 300	Phe G	gc ggc ly Gly	ttg Leu	912
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aag ggc gtt t Lys Gly Val T 35	ac gtt ggg yr Val Gly	cca aat Pro Asn 40	Ala Sei	ctg cgt Leu Arq	g ggc g g Gly A 45	at ttt sp Phe	ggt Gly	144
cgt atc gtg g	tg aaa gat	ggc gcg	aac ati	cag gat	t aat t	gc gtt	atg	192

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gtg Val	ctg Leu	gtg Val	aca Thr	cgc Arg 165	tgt Cys	aag Lys	cag Gln	acg Thr	tta Leu 170	cat His	caa Gln	gtc Val	gag Glu	cca Pro 175	ttg Leu	528	}
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gaa gac gtg atg Glu Asp Val Met	ctc gac cgc ccc Leu Asp Arg Pro 325	g gaa tac tgg c o Glu Tyr Trp G 330	aa agc cac tac In Ser His Tyr 335	cac 1008 His
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caa tgg gtc gga Gln Trp Val Gly 35	Phe Ala Gly Al	ca aat ctg gtg o La Asn Leu Val 1 10	ctg gta gcc aac Leu Val Ala Asn 45	gat 144 Asp

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			ggt ggc gtt ccg gtg a Gly Gly Val Pro Val 2 110	
			aat ggc aaa caa caa Asn Gly Lys Gln Gln : 125	
			atc gca gca ttt aac o Ile Ala Ala Phe Asn i 140	
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		Leu Glu Leu	gtg tgg atg ggg ctg o Val Trp Met Gly Leu i 60	

Pro 65	ctg Leu	gcg Ala	ggc Gly	gca Ala	cag Gln 70	ccg Pro	cct Pro	aac Asn	gtg Val	att Ile 75	atc Ile	ggt Gly	act Thr	atc Ile	gtc Val 80	240
ggc Gly	acg Thr	gcg Ala	ttt Phe	gcc Ala 85	att Ile	act Thr	act Thr	ggc Gly	gtg Val 90	aaa Lys	ccc Pro	gat Asp	gtc Val	gca Ala 95	gta Val	288
ggt Gly	gtc Val	gcc Ala	gta Val 100	cct Pro	ttc Phe	gct Ala	gtc Val	gca Ala 105	gta Val	cag Gln	atg Met	ggg Gly	att Ile 110	acc Thr	ttc Phe	336
ctg Leu	ttc Phe	tcg Ser 115	gtg Val	atg Met	tcc Ser	ggc Gly	gtg Val 120	atg Met	tct Ser	cgc Arg	tgc Cys	gac Asp 125	ctg Leu	gca Ala	aca Thr	384
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gtg Met 1	cat His	tgc Cys	Tyr	Asn	Gly	Met acg	Thr	Gly aag	Leu 10 cgc	His	His tgg	Arg ctg	Glu gaa	Pro 15 ctg	Gly	48 96
gtg Met 1 atg Met	cat His gtt Val	tgc Cys ggc Gly	Tyr gcg Ala 20 cat	Asn 5 gga	Gly tta Leu gtg	Met acg Thr	Thr gac Asp	aag Lys 25	Leu 10 cgc Arg	His gcc Ala atg	tgg Trp	ctg Leu	gaa Glu 30 tgt	Pro 15 ctg Leu	Gly ata Ile tgc	
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gtg Met 1 atg Met gcc Ala tgt Cys ggg Gly 65 cac	cat His gtt Val gat Asp gcg Ala 50 atg	tgc Cys ggc Gly ggt Gly 35 aaa Lys ccg Pro	gcg Ala 20 cat His gag Glu gat Asp	Asn 5 gga Gly cat His aga Arg	tta Leu gtg Val atc Ile cgc Arg 70	Met acg Thr cat His gta Val 55 tat Tyr acc	gac Asp ccg Pro 40 ctg Leu acgg Thr	aag Lys 25 gcg Ala atc Ile tta Leu	Leu 10 cgc Arg gca Ala acc Thr tgt Cys	gcc Ala atg Met gac Asp ggt Gly 75	tgg Trp tcg Ser gcg Ala 60 gaa Glu	ctg Leu ctg Leu 45 atg Met gaa Glu	gaa Glu 30 tgt Cys cag Gln gtg Val	ero 15 ctg Leu tgt Cys gca Ala cag Gln	ata Ile tgc Cys gct Ala atg Met. 80 acg	96 144 192
gtg Met 1 atg Met gcc Ala tgt Cys ggg Gly 65 cac His	cat His gtt Val gat Asp gcg Alaa 50 atg Met ggty	tgc Cys ggc Gly ggt Gly 35 aaa Lys ccg Pro	gcg Ala 20 cat His gag Glu gat Asp	Asn 5 gga Gly cat His aga Arg ggt Gly gtc Val	gtg Val atc Ile cgc Arg 70 cgt Arg	Met acg Thr cat His gta Val 55 tat Tyr . acc Thr	Thr gac Asp ccg Pro 40 ctg Leu acg Thr	aag Lys 25 gcg Ala atc Ile tta Leu tct Ser	Leu 10 cgc Arg gca Ala acc Thr tgt Cys ggt Gly 90 atg	gcc Ala atg Met gac Asp ggt Gly 75	tgg Trp tcg Ser gcg Ala 60 gaa Glu ctg Leu	ctg Leu ctg Leu 45 atg Met gaa Glu gcg Ala	gaa Glu 30 tgt Cys cag Gln gtg Val ggc Gly	tgt Cys gca Ala cag Gln agt Ser 95	ata Ile tgc Cys gct Ala atg Met. 80 acg Thr	96 144 192 240

Thr Pr	o Ala 115	Glu	Ala	Ile	His	Met 120	Ala	Ser	Leu	His	Pro 125	Ala	Àrg	Met	
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aga gt Arg Va 145	c gtt	gcg Ala	ctg Leu	gat Asp 150	agc Ser	g1y ggg	cta Leu	cat His	gtg Val 155	caa Gln	caa Gln	atc Ile	tgg Trp	att Ile 160	480
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aac at Asn II															144
ctg co															192
gca tt Ala Ph 65	tt atc he Ile		-				_		_		_	•			. 240
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gac ta Asp Ty	ac ctg yr Leu														336
tcc go Ser G	gc aac ly Asn 115														384
	ta ccg al Pro														432

	130					135					140					
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atg Met	ccc Pro	gca Ala	gaa Glu	acg Thr 165	cac His	gat Asp	cgc Arg	ggc Gly	ttt Phe 170	gcg Ala	atg Met	acc Thr	agc Ser	agc Ser 175	att Ile	528
acc Thr	acc Thr	atg Met	atg Met 180	gcc Ala	agc Ser	tgc Cys	ctc Leu	gcg Ala 185	gtt Val	ttc Phe	gca Ala	cct Pro	gag Glu 190	acg Thr	atc Ile	576
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acc Thr	tca Ser 210	ctg Leu	ggc Gly	gat Asp	ttc Phe	agc Ser 215	gaa Glu	ggt Gly	gtg Val	ttt Phe	ggt Gly 220	tac Tyr	gca Ala	ccg Pro	tgg Trp	672
aaa Lys 225	cgg Arg	atc Ile	gtt Val	tat Tyr	ctc Leu 230	ggt Gly	agc Ser	ggt Gly	ggc Gly	tta Leu 235	cag Gln	ggc Gly	gca Ala	gca Ala	cgc Arg 240	720
gag Glu	tcg Ser	gcg Ala	ctg Leu	aaa Lys 245	gtg Val	ctg Leu	gaa Glu	ctg Leu	acg Thr 250	gcg Ala	ggt Gly	aaa Lys	ctg Leu	gcg Ala 255	gcc Ala	768
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gat Asp	gac Asp	gaa Glu 275	acg Thr	ctg Leu	gtg Val	gtg Val	gta Val 280	ttt Phe	gtc Val	tcc Ser	agc Ser	cac His 285	cct Pro	tac Tyr	acc Thr	864
cgt Arg	cag Gln 290	tat Tyr	gat Asp	ctt Leu	gat Asp	ctg Leu 295	ctg Leu	gct Ala	gaa Glu	ctt Leu	cgc Arg 300	cgt Arg	gac Asp	aac Asn	cag Gln	912
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gcc Ala	ggt Gly	cca Pro	cat His	atc Ile 325	atc Ile	ctg Leu	cca Pro	ccg Pro	tca Ser 330	cgt Arg	cac His	ttt Phe	atc Ile	gac Asp 335	gtt Val	1008
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cag Gln	tcg Ser	ctg Leu 355	cac His	atg Met	ggc Gly	aat Asn	acg Thr 360	ccg Pro	gat Asp	acc Thr	cca Pro	tca Ser 365	gcc Ala	agt Ser	ggc	1104
acc Thr	gtt Val	aac Asn	cgc Arg	gtg Val	gtg Val	caa Gln	ggc Gly	gta Val	atc Ile	att Ile	cat His	ccg Pro	tgg Trp	cag Gln	gca Ala	1152

1155

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Gly Thr Ala	cac ggc His Gly 180	tta tad Leu Tyr	agc Ser	aaa Lys 185	acg Thr	ccg Pro	aag Lys	att Ile	gat Asp 190	ttc Phe	cag Gln	576
cgg ctg gcg Arg Leu Ala 195	gaa att Glu Ile	cgt gaa Arg Glu	gtg Val 200	gtg Val	gat Asp	gtt Val	cct Pro	ctg Leu 205	gtg Val	ctg Leu	cat His	624
ggt gcc agc Gly Ala Ser 210	gat gtt Asp Val	ccg gat Pro Asp 215	Glu	ttt Phe	gtc Val	cgt Arg	cgc Arg 220	act Thr	att Ile	gaa Glu	ctt Leu	672
ggc gtc aca Gly Val Thr 225	aaa gtg Lys Val	aac gtt Asn Val 230	gcc Ala	aca Thr	gaa Glu	tta Leu 235	aaa Lys	ata Ile	gcc Ala	ttc Phe	gct Ala 240	720
ggc gcg gtt Gly Ala Val	aaa gcc Lys Ala 245	tgg tti Trp Phe	gcg Ala	gaa Glu	aat Asn 250	ccg Pro	cag Gln	ggt Gly	aat Asn	gat Asp 255	cct Pro	768
cgt tat tat Arg Tyr Tyr	atg cgc Met Arg 260	gtc gga Val Gly	atg Met	gat Asp 265	gcg Ala	atg Met	aaa Lys	gaa Glu	gtt Val 270	gtc Val	aga Arg	816
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			egt cat cgt cgt Arg His Arg Arg 90		288
gtt cgc ggt cag Val Arg Gly Gln 100	cgt acc aa Arg Thr Ly	g acc aac g s Thr Asn A 105	gca cgt acc cgt Ala Arg Thr Arg	aag ggt ccg Lys Gly Pro 110	336
cgc aaa ccg atc Arg Lys Pro Ile 115	-	a			357
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act atc act gat Thr Ile Thr Asp 35	cgt cag gg Arg Gln Gl	t aac gcg t y Asn Ala I 40	ttg ggt tgg gca Leu Gly Trp Ala 45	aca gcc ggt Thr Ala Gly	144
		r Arg Lys S	tcc act ccg ttt Ser Thr Pro Phe 60		192
gtt gca gca gag Val Ala Ala Glu 65	cgt tgc gc Arg Cys Al 70	t gac gcc g a Asp Ala N	gtg aaa gaa tac Val Lys Glu Tyr 75	ggc atc aag Gly Ile Lys 80	240
			ggt cca ggc cgc Gly Pro Gly Arg 90		288
	Asn Ala Al		cgc atc act aac Arg Ile Thr Asn		336
gtg act ccg atc Val Thr Pro Ile 115	cct cat aa Pro His As	c ggt tgt d n Gly Cys <i>H</i> 120	cgt ccg ccg aaa Arg Pro Pro Lys 125	aaa cgt cgc Lys Arg Arg	384
gta taa Val *					390

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195 200 205

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ggc aca atc gat Gly Thr Ile Asp 210	cct gaa gag Pro Glu Glu 215	gcg att cgt Ala Ile Arg	cgt gcg gca acc Arg Ala Ala Thr 220	att ctg 672 Ile Leu
gct gaa caa ctg Ala Glu Gln Leu 225	gaa gct ttc Glu Ala Phe 230	gtt gac tta Val Asp Leu	cgt gat gta cgt Arg Asp Val Arg 235	cag cct 720 Gln Pro 240
gaa gtg aaa gaa Glu Val Lys Glu	gag aaa cca Glu Lys Pro 245	gag ttc gat Glu Phe Asp 250	ccg atc ctg ctg Pro Ile Leu Leu	cgc cct 768 Arg Pro 255
gtt gac gat ctg Val Asp Asp Leu 260	gaa ttg act Glu Leu Thr	gtc cgc tct Val Arg Ser 265	gct aac tgc ctt Ala Asn Cys Leu 270	aaa gca 816 Lys Ala
gaa gct atc cac Glu Ala Ile His 275	tat atc ggt Tyr Ile Gly	gat ctg gta Asp Leu Val 280	cag cgt acc gag Gln Arg Thr Glu 285	gtt gag 864 Val Glu
ctc ctt aaa acg Leu Leu Lys Thr 290	cct aac ctt Pro Asn Leu 295	ggt aaa aaa Gly Lys Lys	tct ctt act gag Ser Leu Thr Glu 300	att aaa 912 Ile Lys
gac gtg ctg gct Asp Val Leu Ala 305	tcc cgt gga Ser Arg Gly 310	ctg tct ctg Leu Ser Leu	ggc atg cgc ctg Gly Met Arg Leu 315	gaa aac 960 Glu Asn 320
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atc atc aag acg Ile Ile Lys Thr 35	act ctg cct Thr Leu Pro	aaa gcg aaa Lys Ala Lys 40	gag ctg cgc cgc Glu Leu Arg Arg 45	gta gtt 144 Val Val

Glu Pro Leu 50	att act Ile Thr	_	Lys		-	_	-	-		_	_	192
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aac gaa ctg Asn Glu Leu	ggc ccg Gly Pro 85	cgt tto Arg Pho	gcg Ala	agc Ser	cgt Arg 90	gcc Ala	ggt Gly	ggt Gly	tac Tyr	act Thr 95	cgt Arg	288
att ctg aag Ile Leu Lys	tgt ggc Cys Gly 100	ttc cg	gca Ala	ggc Gly 105	gac Asp	aac Asn	gcg Ala	ccg Pro	atg Met 110	gct Ala	tac Tyr	336
atc gag ctg Ile Glu Leu 115											taa *	384
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gcg ctg att Ala Leu Ile												96
	20		_	25	GIN	Pro	Leu	Pne	Ala 30	Ala	Leu	
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Phe Pro Gln	ctg cca Leu Pro	cga cc Arg Pro	gtt Val 40 gctg	25 tat Tyr gtg	cag Gln gga	caa Gln att	gaa Glu tcg	agt Ser 45	30 ttt Phe ttg	gca Ala ttt	gct Ala gcg	144 192
Phe Pro Gln 35 ctg gca ctg Leu Ala Leu	ctg cca Leu Pro gct cat Ala His	cga cc Arg Pr ttc tg Phe Tr 5	g ctg	25 tat Tyr gtg Val	cag Gln gga Gly	caa Gln att Ile	gaa Glu tcg Ser 60	agt Ser 45 agt Ser	30 ttt Phe ttg Leu	gca Ala ttt Phe	gct Ala gcg Ala	
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Phe Pro Gln 35 ctg gca ctg Leu Ala Leu 50 gtg atc att Val Ile Ile 65 gcg gaa ttt	ctg cca Leu Pro gct cat Ala His ggc act Gly Thr cgc cca Arg Pro 85	cga cc Arg Protection of the tree tree tree tree tree tree tree	g gtt Val 40 g ctg Leu g gga Gly g gaa L Glu	tat Tyr gtg Val att Ile act Thr	cag Gln gga Gly gct Ala att Ile 90 gcc	caa Gln att Ile gtc Val 75 gcc Ala	gaa Glu tcg Ser 60 act Thr gcc Ala	agt Ser 45 agt Ser cgc Arg gtt Val	ttt Phe ttg Leu ccg Pro gga Gly	gca Ala ttt Phe tgg Trp cag Gln 95	gct Ala gcg Ala ggc Gly 80 act Thr	192 240

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atc Ile 225	atc Ile	gca Ala	gac Asp	cgc Arg	ctg Leu 230	ttt Phe	gaa Glu	agg Arg	ctg Leu	gtg Val 235	cag Gln	gcg Ala	ctt Leu	agc Ser	cag Gln 240		720
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cgt Arg	atc Ile	gac Asp 115	gaa Glu	tta Leu	atg Met	gcg Ala	cta Leu 120	ctg Leu	GJA GGG	ctg Leu	gag Glu	tca Ser 125	aat Asn	ttg Leu	cgt Arg		384
gag Glu	cgt Arg 130	tat Tyr	ccg Pro	cat His	cag Gln	ctt Leu 135	tcc Ser	ggt Gly	ggt Gly	cag Gln	cag Gln 140	caa Gln	cgt Arg	gtg Val	gga Gly		432
gtg Val 145	gcg Ala	cgt Arg	gca Ala	ctg Leu	gct Ala 150	gcc Ala	gat Asp	ccg Pro	caa Gln	gtc Val 155	tta Leu	cta Leu	atg Met	gat Asp	gaa Glu 160		480
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gat Asp	cac His 210	ggt Gly	gaa Glu	gta Val	gtg Val	cag Gln 215	cag Gln	ggc Gly	aat Asn	ccg Pro	ctg Leu 220	acg Thr	atg Met	ctg Leu	act Thr		672
cgt Arg 225	ccg Pro	gcg Ala	aat Asn	gat Asp	ttt Phe 230	gtc Val	cgc Arg	cag Gln	ttt Phe	ttt Phe 235	gga Gly	cgt Arg	agt Ser	gaa Glu	ctg Leu 240		720
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170

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165

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			gtc Val													864
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			gcg Ala													960
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			gcg Ala 340													1056
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gac Asp	gcg Ala 370	ctg Leu	ttc Phe	gat Asp	ttg Leu	ctt Leu 375	Ile	gca Ala	ctg Leu	ctg Leu	aag Lys 380	gtg Val	aaa Lys	cgt Arg	aat Asn	1152
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gtg Val	agc Ser	ctg Leu	ccg Pro 20	cta Leu	cag Gln	gcg Ala	gct Ala	tcc Ser 25	ccc Pro	gtt Val	aaa Lys	gtc Val	ggt Gly 30	tca Ser	aaa Lys	96
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gcg Ala	ttt Phe	gaa Glu	aaa Lys 180	gcc Ala	tat Tyr	ggc Gly	ttt Phe	aag Lys 185	ctc Leu	ggt Gly	cag Gln	gat Asp	cag Gln 190	ttg Leu	ctg Leu	576
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gat Asp	gcc Ala 290	aaa Lys	aaa Lys	gtg Val	gct Ala	gcc Ala 295	gac Asp	tac Tyr	ctg Leu	aaa Lys	caa Gln 300	aaa Lys	ggg Gly	tgg Trp	acg Thr	912
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	Arg Leu 85		ys Trp	Met	Leu 90	Pro	Val	Leu	Asp	Ala 95	Val	
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gaa gcc ggt Glu Ala Gly 115	Pro Leu	atc go Ile A	cg gtt la Val 120	tgt Cys	atg Met	ggc Gly	gtc Val	att Ile 125	act Thr	ggc Gly	gtt Val	384
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tgg cat ctt Trp His Let 195	Lys Leu	ccg a Pro T	cg ttt hr Phe 200	Ala	ctg Leu	gat Asp	gag Glu	aat Asn 205	ggg Gly	cgt Arg	tga *	624
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gaa Glu	caa Gln	att Ile 115	gcc Ala	aat Asn	gcg Ala	tta Leu	cgt Arg 120	caa Gln	ctg Leu	gcc Ala	ccc Pro	tgg Trp 125	agt Ser	ccg Pro	caa Gln	3	84
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agt Ser	gac Asp	tgg Trp	ttt Phe	gaa Glu 245	cgt Arg	gca Ala	agc Ser	cca Pro	cgt Arg 250	att Ile	atc Ile	ctc Leu	gct Ala	gca Ala 255	caa Gln	7	68
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cgt Arg	gac Asp	aaa Lys	atc Ile 20	gaa Glu	aac Asn	cgt Arg	caa Gln	act Thr 25	atc Ile	agt Ser	ctc Leu	ggc Gly	ggt Gly 30	Cys	gaa Glu	!	96
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ggc Gly	atc Ile 50	ggt Gly	aaa Lys	gtc Val	gct Ala	gcg Ala 55	gcg Ala	ctg Leu	ggt Gly	gcc Ala	act Thr 60	ttg Leu	ctg Leu	ttg Leu	gaa Glu	1	92
cac His 65	tgc Cys	aag Lys	cca Pro	gat Asp	gtg Val 70	att Ile	att Ile	aac Asn	acc Thr	ggt Gly 75	tct Ser	gcc Ala	ggt Gly	ggc Gly	ctg Leu 80		40
gca Ala	cca Pro	acg Thr	ttg Leu	aaa Lys 85	gtg Val	ggc Gly	gat Asp	atc Ile	gtt Val 90	gtc Val	tcg Ser	gac Asp	gaa Glu	gca Ala 95	cgt Arg	2	88
tat Tyr	cac His	gac Asp	gcg Ala 100	gat Asp	gtc Val	acg Thr	gca Ala	ttt Phe 105	ggt Gly	tat Tyr	gaa Glu	tac Tyr	ggt Gly 110	cag Gln	tta Leu	3	36
cca Pro	ggc Gly	tgt Cys 115	ccg Pro	gca Ala	ggc Gly	ttt Phe	aaa Lys 120	gct Ala	gac Asp	gat Asp	aaa Lys	ctg Leu 125	atc Ile	gct Ala	gcc Ala	3	84
gct Ala	gag Glu 130	gcc Ala	tgc Cys	att Ile	gcc Ala	gaa Glu 135	ctg Leu	aat Asn	ctt Leu	aac Asn	gct Ala 140	gta Val	cgt Arg	ggc Gly	ctg′ Leu	4	32
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atc Ile	cgc Arg	cac His	aac Asn	ttc Phe 165	cca Pro	cag Gln	gcc Ala	att Ile	gct Ala 170	gta Val	gag Glu	atg Met	gaa Glu	gcg Ala 175	acg Thr	5	28
gca Ala	atc Ile	gcc Ala	cat His 180	gtc Val	tgc Cys	cac His	aat Asn	ttc Phe 185	aac Asn	gtc Val	ccg Pro	ttt Phe	gtt Val 190	gtc Val	gta Val	5	76
cgc Arg	gcc Ala	atc Ile 195	tcc Ser	gac Asp	gtg Val	gcc Ala	gat Asp 200	caa Gln	cag Gln	tct Ser	cat His	ctt Leu 205	agc Ser	ttc Phe	gat Asp	6	24
gag Glu	ttc Phe 210	ctg Leu	gct Ala	gtt Val	gcc Ala	gct Ala 215	aaa Lys	cag Gln	tcc Ser	agc Ser	ctg Leu 220	Met	gtt Val	gag Glu	tca Ser		72
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	gcg Ala															96
	ccc Pro															144
	gtg Val 50															192
	gcc Ala															240
ccg Pro	acc Thr	cgt Arg	gtg Val	gaa Glu 85	atc Ile	ggc Gly	gat Asp	cgt Arg	aac Asn 90	cgc Arg	att Ile	cgc Arg	gaa Glu	agc Ser 95	gtc Val	288
	att Ile															336
	gac Asp															384
	ggt Gly 130															432
	tcg Ser															480
cag Gln	ttc Phe	tgc Cys	atc Ile	att Ile 165	ggt Gly	gcg Ala	cac His	gtg Val	atg Met 170	gtt Val	ggc Gly	ggc Gly	tgc Cys	tcc Ser 175	ggt Gly	528
	gcg Ala															576

acg ccg tt Thr Pro Ph	tc ggt ne Gly 95	gtc (Val)	aat Asn	Ile	gaa Glu 200	ggg Gly	ctg Leu	aag Lys	cgc Arg	cgc Arg 205	gga Gly	ttc Phe	agc Ser		524
cgt gag go Arg Glu Al 210	cg att la Ile	acc f	Ala	atc Ile 215	cgc Arg	aat Asn	gcg Ala	tat Tyr	aag Lys 220	ctg Leu	att Ile	tat Tyr	cgt Arg	•	572
agc ggt ag Ser Gly Ly 225	aa acg ys Thr	Leu	gat Asp 230	gaa Glu	gtg Val	aaa Lys	ccg Pro	gaa Glu 235	att Ile	gct Ala	gaa Glu	ctg Leu	gcg Ala 240	7	720
gaa aca ta Glu Thr T	at ccg yr Pro	gaa Glu 245	gtg Val	aaa Lys	gcc Ala	ttt Phe	acc Thr 250	gat Asp	ttc Phe	ttt Phe	gca Ala	cgc Arg 255	tca Ser	-	768
acg cgc g Thr Arg G														•	789
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tcc ggc g Ser Gly A	at atc sp Ile 20	Leu	ggg Gly	gcc Ala	ggt Gly	tta Leu 25	atc Ile	cgc Arg	gct Ala	ctg Leu	aaa Lys 30	gaa Glu	cat His		96
gtg ccc a Val Pro A	ac gcc sn Ala 35	cgc Arg	ttt Phe	gtt Val	ggt Gly 40	gtt Val	gcc Ala	ggg Gly	cca Pro	cga Arg 45	atg Met	cag Gln	gct Ala		144
gaa ggc t Glu Gly C 50	gc gaa Cys Glu	gcc Ala	tgg Trp	tac Tyr 55	gaa Glu	atg Met	gaa Glu	gaa Glu	ctg Leu 60	Ala	gtg Val	atg Met	ggc Gly		192
att gtt g Ile Val G 65	gaa gtg Slu Val	ctc Leu	ggt Gly 70	cgt Arg	ctg Leu	cgt Arg	cgc Arg	tta Leu 75	ctg Leu	cat His	att Ile	cgt	gcc Ala 80		240
gat ctg a Asp Leu 1	aca aag Thr Lys	cgt Arg 85	ttt Phe	ggc	g aa Glu	ctg Leu	aag Lys 90	Pro	gat Asp	gtt Val	ttt Phe	gtt Val 95	Gly	•	288
att gat o	gcg cct Ala Pro 100	Asp	ttc Phe	aat Asn	att Ile	act Thr 105	Leu	gaa Glu	ggt Gly	aac Asn	Leu 110	Lys	aag Lys		336
cag ggt a	atc aaa	acc	att	cat	tac	gto	agt	ccg	tca	gtc	tgg	gcg	tgg		384

Gln	Gly	Ile 115	Lys	Thr	Ile	His	Tyr 120	Val	Ser	Pro	Ser	Val 125	Trp	Ala	Trp	
cga Arg	cag Gln 130	aaa Lys	cgt Arg	gtt Val	ttc Phe	aaa Lys 135	ata Ile	ggc Gly	aga Arg	gcc Ala	acc Thr 140	gat Asp	ctg Leu	gtg Val	ctc Leu	432
gca Ala 145	ttt Phe	ctg Leu	cct Pro	ttc Phe	gaa Glu 150	aaa Lys	gcg Ala	ttt Phe	tat Tyr	gac Asp 155	aaa Lys	tac Tyr	aac Asn	gta Val	ccg Pro 160	480
tgc Cys	cgc Arg	ttt Phe	atc Ile	ggt Gly 165	cat His	acc Thr	atg Met	gct Ala	gat Asp 170	gcc Ala	atg Met	cca Pro	tta Leu	gat Asp 175	cca Pro	528
gat Asp	aaa Lys	aat Asn	gcc Ala 180	gcc Ala	cgt Arg	gat Asp	gtg Val	ctg Leu 185	ggg Gly	atc Ile	cct Pro	cac His	gat Asp 190	gcc Ala	cac His	576
tgc Cys	ctg Leu	gcg Ala 195	ttg Leu	cta Leu	ccg Pro	ggg Gly	agc Ser 200	cgt Arg	ggt Gly	gca Ala	gaa Glu	gtt Val 205	gaa Glu	atg Met	ctt Leu	624
agt Ser	gcc Ala 210	gat Asp	ttc Phe	ctg Leu	aaa Lys	acg Thr 215	gcc Ala	cag Gln	ctt Leu	ttg Leu	cgc Arg 220	cag Gln	aca Thr	tat Tyr	ccg Pro	672
gat Asp 225	ctc Leu	gaa Glu	atc Ile	gtg Val	gtg Val 230	cca Pro	ctg Leu	gtg Val	aat Asn	gcc Ala 235	aaa Lys	cgc Arg	cgc	gag Glu	cag Gln 240	720
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ctg Leu	gat Asp	Gly	atg Met 260	ggc Gly	cgt Arg	gag Glu	gcg Ala	atg Met 265	gtc Val	gcc Ala	agc Ser	gat Asp	gcg Ala 270	gcg Ala	cta Leu	816
ctg Leu	gcg Ala	tcg Ser 275	ggt Gly	acg Thr	gca Ala	gcc Ala	ctg Leu 280	Glu	tgt Cys	atg Met	ctg Leu	gcg Ala 285	aaa Lys	tgc Cys	ccg Pro	864
atg Met	gtg Val 290	gtg Val	gga Gly	tat Tyr	cgc Arg	atg Met 295	aag Lys	cct Pro	ttt Phe	acc Thr	ttc Phe 300	tgg Trp	ttg Leu	gcg Ala	aag Lys	912
cgg Arg 305	ctg Leu	gtg Val	aaa Lys	act Thr	gat Asp 310	tat Tyr	gtc Val	tcg Ser	ctg Leu	cca Pro 315	Asn	ctg Leu	ctg Leu	gcg Ala	ggc Gly 320	960
aga Arg	gag Glu	tta Leu	gtc Val	aaa Lys 325	gaa Glu	tta Leu	ttg Leu	cag Gln	gaa Glu 330	Glu	tgt Cys	gag Glu	ccg Pro	caa Gln 335	aaa Lys	1008
ctg Leu	gct Ala	gcg Ala	gcg Ala 340	Leu	tta Leu	ccg Pro	ctg Leu	ttg Leu 345	Ala	aac Asn	ggg	aaa Lys	acc Thr 350	Ser	cac His	1056
gcg	atg	cac	gat	acc	ttc	cgt	gaa	ctg	cat	cag	cag	ato	cgc	tgc	aat	1104

Ala Met His As	p Thr Phe A	arg Glu Leu 360	His Gln (Gln Ile Arg 365	Cys Asn	
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ctg agc gaa aa Leu Ser Glu Ly 50						192
gcg ttg agc tg Ala Leu Ser Tr 65						240
ctg aac att ct Leu Asn Ile Le						288
ggg ctg cat at Gly Leu His Il 10	e Ala Pro G					336
ccg aaa tta cc Pro Lys Leu Pr 115						384
gta ccg gaa at Val Pro Glu Il 130	e Ser Ala A		Leu Ala			432
gcc gaa atg gc Ala Glu Met Al 145	g gcg ctg g a Ala Leu <i>P</i> 150	gat att gtt Asp Ile Val	ttc ccg of Phe Pro 0 155	caa tat ggt Gln Tyr Gly	ttt gcc Phe Ala 160	480
caa cac aaa go Gln His Lys Gl						528

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gcg ttg ggt atg Ala Leu Gly Met 35	cca gca ctg Pro Ala Leu	gcg atc acc gat Ala Ile Thr Asp 40	ttc acc aac c Phe Thr Asn L 45	tt tgt 144 eu Cys
ggt ctg gtg aag Gly Leu Val Lys 50	ttc tac gga Phe Tyr Gly 55	gcg gga cat ggc Ala Gly His Gly	gca ggg att a Ala Gly Ile L 60	ag cct 192 ys Pro
atc gtc ggg gca Ile Val Gly Ala 65	gat ttt aac Asp Phe Asn 70	gtc cag tgc gac Val Gln Cys Asp 75	Leu Leu Gly A	at gag 240 sp Glu 80
tta acc cac ctg Leu Thr His Leu	acg gta ctg Thr Val Leu 85	gcg gcg aac aat Ala Ala Asn Asn 90	Thr Gly Tyr G	ag aat 288 ln Asn 95
	Ile Ser Lys	gcg tat cag cgc Ala Tyr Gln Arg 105		
ggg ccg atc atc Gly Pro Ile Ile 115	gat cgc gac Asp Arg Asp	tgg ctt atc gaa Trp Leu Ile Glu 120	tta aac gaa g Leu Asn Glu G 125	gg ttg 384 ly Leu
atc ctt ctt tcc Ile Leu Leu Ser 130	ggc gga cgc Gly Gly Arg 135	atg ggc gac gtc Met Gly Asp Val	gga cgc agt c Gly Arg Ser L 140	tt ttg 432 eu Leu
		gat gag tgt gtc Asp Glu Cys Val 155	Ala Phe Tyr G	

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ggt Gly	ttg Leu	ccc Pro 195	gtc Val	gtg Val	gcg Ala	acc Thr	aac Asn 200	gac Asp	gtg Val	cgc Arg	ttt Phe	atc Ile 205	gac Asp	agc Ser	agc Ser	624
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ctc Leu 225	gac Asp	gat Asp	cct Pro	aaa Lys	cgc Arg 230	ccg Pro	cgt Arg	aac Asn	tat Tyr	tcg Ser 235	ccg Pro	cag Gln	caa Gln	tat Tyr	atg Met 240	720
cgt Arg	agc Ser	gaa Glu	gag Glu	gag Glu 245	atg Met	tgt Cys	gag Glu	ctg Leu	ttt Phe 250	gcc Ala	gac Asp	atc Ile	Pro	gaa Glu 255	gcc Ala	768
					gag Glu											816
ctt Leu	ggt Gly	gaa Glu 275	tac Tyr	ttc Phe	ctg Leu	ccg Pro	cag Gln 280	ttc Phe	ccg Pro	acc Thr	ggg Gly	gac Asp 285	atg Met	agc Ser	acc Thr	864
					aag Lys											912
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gac Asp 385	ctg Leu	ctg Leu	ttc Phe	gaa Glu	cgt Arg 390	ttc Phe	ctt Leu	aac Asn	ccg Pro	gaa Glu 395	cgt Arg	gtc Val	tcc Ser	atg Met	cct Pro 400	1200

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	gta Val															1	1296
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cct Pro 625	gac Asp	Cys Cys	ttc Phe	gaa Glu	gat Asp 630	Met	atc Ile	gcc Ala	cta Leu	gtg Val 635	gca Ala	ctg Leu	ttc Phe	cgc Arg	ccc Pro 640	:	1920

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tat Tyr	ggt Gly	att Ile 835	ggc Gly	gcg Ala	atc Ile	aaa Lys	ggg Gly 840	gtc Val	ggt Gly	gaa Glu	ggt Gly	ccg Pro 845	att Ile	gag Glu	gcc Ala	254	4 .
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ctc Leu 865	tgc Cys	gcc Ala	cgt Arg	acc Thr	gac Asp 870	acc Thr	aaa Lys	aag Lys	ttg Leu	aac Asn 875	cgt Arg	cgc Arg	gtg Val	ctg Leu	gaa Glu 880	264	0

:>

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acg ga Thr As	ac agg sp Arg 190	caa Gln	att Ile	gat Asp	gac Asp 109	Gln	ctt Leu	tta Leu	aac Asn	cga Arg 110	Leu	cgt Arg	cag Gln	tct Ser	3312
ctg ga Leu G 1105	aa ccc Lu Pro	cac His	cgc Arg	tct Ser 111	Gly	aca Thr	att Ile	cca Pro	gta Val 111	His	ctc Leu	tac Tyr	tat Tyr	cag Gln 1120	3360

agg gcg gat gca cgc gcg cgg ttg cgt ttt ggc gcg acg tgg cgt gtc Arg Ala Asp Ala Arg Ala Arg Leu Arg Phe Gly Ala Thr Trp Arg Val 1125 1130 1135	3408
tct ccg agc gat cgt tta tta aac gat ctc cgt ggc ctc att ggt tcg Ser Pro Ser Asp Arg Leu Leu Asn Asp Leu Arg Gly Leu Ile Gly Ser 1140 1145 1150	3456
gag cag gtg gaa ctg gag ttt gac taa Glu Gln Val Glu Leu Glu Phe Asp * 1155 1160	3483
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aga atg gca cga gac tcc gtg ctg cta ctg gaa aaa ctc ggc tgt cgc Arg Met Ala Arg Asp Ser Val Leu Leu Glu Lys Leu Gly Cys Arg 20 . 25 . 30	96
gta aat ttc ccg gag aaa cag gga tgc tgc ggt cag cct gcg atc aat Val Asn Phe Pro Glu Lys Gln Gly Cys Cys Gly Gln Pro Ala Ile Asn 35 40 45	144
agc ggt tat atc aaa gaa gcg att cca ggg atg aaa aat ctg atc gcc Ser Gly Tyr Ile Lys Glu Ala Ile Pro Gly Met Lys Asn Leu Ile Ala 50 55 60	192
gca ctg gag gat aac gac gat ccc att att tca ccg gct ggc tct tgc Ala Leu Glu Asp Asn Asp Pro Ile Ile Ser Pro Ala Gly Ser Cys 65 70 75 80	240
acc tat gcc gta aaa agt tac ccg acg tat ctg gcg gat gaa cct gaa Thr Tyr Ala Val Lys Ser Tyr Pro Thr Tyr Leu Ala Asp Glu Pro Glu 85 90 95	288
tgg gca tca cgt gcc gca aag gtt gcc gcg cgt atg cag gat ctc acc Trp Ala Ser Arg Ala Ala Lys Val Ala Ala Arg Met Gln Asp Leu Thr 100 105 110	336
tct ttt att gtt aat aaa tta ggg gta gtc gat gta ggt gcc agt ttg Ser Phe Ile Val Asn Lys Leu Gly Val Val Asp Val Gly Ala Ser Leu 115 120 125	384
caa ggg aga gcg gtg tat cac cca tct tgt agc ctg gcc cgt aag ctg Gln Gly Arg Ala Val Tyr His Pro Ser Cys Ser Leu Ala Arg Lys Leu 130 135 140	432

Gly Val Lys 145	gac gag Asp Glu											480
gag ctg ttg Glu Leu Leu												528
acg ttc tcg Thr Phe Ser												576
aag gtt gcg Lys Val Ala 195			Glu V									624
gac gtg agt Asp Val Ser 210	-	Leu i		_		_				-		672
cag aaa gtc Gln Lys Val 225		_		_	-		_	_	_	-	tga *	720
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Ile	Leu	Gln	Val	Ala	Gln	Arg	Lys	Asn 105	Ala	Arg	Lys	Val	Val 110	Lys	Ser	
aaa Lys	tcg Ser	atg Met 115	gtg Val	acc Thr	gaa Glu	gag Glu	att Ile 120	ggt Gly	gtc Val	aat Asn	cat His	gtg Val 125	ttg Leu	cag Gln	gat Asp	384
gct Ala	ggc Gly 130	att Ile	cag Gln	gtg Val	att Ile	gaa Glu 135	acc Thr	gat Asp	ctg Leu	ggt Gly	gaa Glu 140	tat Tyr	att Ile	ctc Leu	cag Gln	432
ctg Leu 145	gat Asp	caa Gln	gat Asp	ccg Pro	cca Pro 150	tct Ser	cat His	gtt Val	gtg Val	gtc Val 155	ccg Pro	gca Ala	att Ile	cat His	aaa Lys 160	480
gat Asp	cgc Arg	cat His	cag Gln	atc Ile 165	cgt Arg	cga Arg	gtg Val	cta Leu	cac His 170	gaa Glu	cgt Arg	ctg Leu	ggc Gly	tat Tyr 175	gag Glu	528
Gly	ccg Pro	gaa Glu	acg Thr 180	cct Pro	gaa Glu	gcg Ala	atg Met	acc Thr 185	tta Leu	ttc Phe	atc Ile	cgg Arg	caa Gln 190	aaa Lys	atc Ile	576
cgc Arg	gaa Glu	gat Asp 195	ttc Phe	ctc Leu	agt Ser	gct Ala	gaa Glu 200	ata Ile	ggt Gly	att Ile	acc Thr	ggc Gly 205	tgt Cys	aat Asn	ttc Phe	624
gcg Ala	gtg Val 210	gca Ala	gag Glu	acc Thr	ggt Gly	tcg Ser 215	gta Val	tgc Cys	ctg Leu	gtg Val	acc Thr 220	aat Asn	gaa Glu	ggt Gly	aat Asn	672
gcg Ala 225	cga Arg	atg Met	tgt Cys	acc Thr	acg Thr 230	ctg Leu	cct Pro	aaa Lys	acg Thr	cat His 235	att Ile	gca Ala	gtg Val	atg Met	gga Gly 240	720
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atg Met	ctg Leu	gcg Ala	cgc Arg 260	Ser	gcc Ala	gtt Val	ggt Gly	gca Ala 265	Arg	ttg Leu	acg Thr	gga Gly	tac Tyr 270	aac Asn	acc Thr	816
tgg Trp	ctg Leu	aca Thr 275	Gly	ccg Pro	cgc Arg	gaa Glu	gct Ala 280	Gly	cac His	gtt Val	gat Asp	ggt Gly 285	cct Pro	gaa Glu	gag Glu	864
ttt Phe	cat His 290	Leu	gtt Val	att Ile	gtc Val	gat Asp 295	aac Asn	ggg Gly	cgt Arg	tct Ser	gag Glu 300	Val	ctg Leu	gcc Ala	tct Ser	912
gaa Glu 305	Phe	cgg Arg	gat Asp	gtg Val	ctg Leu 310	Arg	tgt Cys	att	cgc	tgc Cys 315	Gly	gct	tgt Cys	atg Met	aat Asn 320	960
act Thr	tgt Cys	ccg	gca Ala	tat Tyr 325	Arg	cat His	att Ile	ggc Gly	ggt Gly 330	His	gga Gly	tat Tyr	ggc Gly	tct Ser 335	att	1008
tat	cca	ggg	сса	att	ggt	gcg	gtg	att	tct	ccg	cta	ctt	ggc	ggc	tat	1056

Tyr	Pro	Gly	Pro 340	Ile	Gly	Ala	Val	Ile 345	Ser	Pro	Leu	Leu	Gly 350	Gly	Tyr	
					tta Leu											1104
gac Asp	aac Asn 370	gtg Val	tgt Cys	ccg Pro	gtg Val	cgt Arg 375	att Ile	ccg Pro	ctg Leu	tca Ser	aaa Lys 380	ctg Leu	att Ile	ttg Leu	cgt Arg	1152
cat His 385	cgt Arg	cgg Arg	gtg Val	atg Met	gct Ala 390	gaa Glu	aaa Lys	ggg Gly	atc Ile	acc Thr 395	gca Ala	aaa Lys	gca Ala	gag Glu	caa Gln 400	1200
cgg Arg	gcg Ala	ata Ile	aaa Lys	atg Met 405	ttc Phe	gct Ala	tat Tyr	gcc Ala	aat Asn 410	agt Ser	cat His	cca Pro	gga Gly	ttg Leu 415	tgg Trp	1248
aaa Lys	gtc Val	ggg Gly	atg Met 420	atg Met	gcc Ala	ggt Gly	gct Ala	cat His 425	gcg Ala	gca Ala	agc Ser	tgg Trp	ttt Phe 430	atc Ile	aat Asn	1296
ggc Gly	ggc Gly	aaa Lys 435	aca Thr	cca Pro	ctc Leu	aaa Lys	ttt Phe 440	ggc Gly	gcg Ala	att Ile	agc Ser	gac Asp 445	tgg Trp	atg Met	gaa Glu	1344
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_			_	-	cag Gln 470			_								1428
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					gcg Ala											96
ctg Leu	acg Thr	gag Glu 35	aga Arg	gtt Val	tcc Ser	gta Val	gtt Val 40	ggt Gly	tta Leu	aga Arg	aac Asn	atc Ile 45	agg Arg	cgc Arg	agg Arg	144
aga Arg	aaa Lys	aga Arg	atg Met	gat Asp	aat Asn	cga Arg	ggc Gly	gaa Glu	ttt Phe	ttg Leu	aat Asn	aac Asn	gtt Val	gct Ala	cag Gln	192

	50					55					60						
gca Ala 65	ctg Leu	ggt Gly	cgc Arg	ccg Pro	ctg Leu 70	cga Arg	ctt Leu	gaa Glu	ccg Pro	caa Gln 75	gca Ala	gaa Glu	gat Asp	gcg Ala	ccg Pro 80		240
ctt Leu	aac Asn	aac Asn	tat Tyr	gct Ala 85	aac Asn	gag Glu	cgg Arg	ctt Leu	acc Thr 90	caa Gln	ctt Leu	aac Asn	caa Gln	cag Gln 95	cag Gln		288
cgc Arg	tgt Cys	gac Asp	gcg Ala 100	ttt Phe	att Ile	cag Gln	ttt Phe	gcc Ala 105	agc Ser	gat Asp	gtt Val	atg Met	ttg Leu 110	acg Thr	cgc Arg		336
tgt Cys	gag Glu	ctg Leu 115	acc Thr	agc Ser	gag Glu	gcg Ala	aag Lys 120	gcg Ala	gca Ala	gaa Glu	gct Ala	gca Ala 125	ata Ile	cgt Arg	ctg Leu		384
tgt Cys	aaa Lys 130	gag Glu	ctg Leu	gga Gly	gat Asp	cag Gln 135	tcg Ser	gtc Val	gtg Val	att Ile	agc Ser 140	ggt Gly	gac Asp	acg Thr	agg Arg	*	432
ctg Leu 145	gag Glu	gaa Glu	ttg Leu	Gly	att Ile 150	agc Ser	gaa Glu	cgt Arg	ttg Leu	cag Gln 155	cag Gln	gaa Glu	tgc Cys	aat Asn	gcc Ala 160		480
gtt Val	gtt Val	tgg Trp	gat Asp	ccg Pro 165	gcg Ala	aaa Lys	ggt Gly	gcc Ala	gag Glu 170	aat Asn	atc Ile	tcg Ser	cag Gln	gca Ala 175	gag Glu		528
cag Gln	gct Ala	aaa Lys	gtg Val 180	ggt Gly	gtt Val	gtg Val	tat Tyr	gct Ala 185	gaa Glu	tat Tyr	ggt Gly	tta Leu	acc Thr 190	gaa Glu	tcg Ser		576
gga Gly	ggc Gly	gtg Val 195	gtt Val	ctt Leu	ttt Phe	tcc Ser	gcc Ala 200	gcc Ala	gag Glu	cgc Arg	ggg Gly	cgt Arg 205	tca Ser	ttg Leu	agc Ser		624
ctg Leu	ctc Leu 210	ccg Pro	gaa Glu	tat Tyr	tct Ser	ctt Leu 215	ttt Phe	atc Ile	ctg Leu	cgt Arg	aaa Lys 220	agc Ser	act Thr	atc Ile	ctg Leu		672
ccg Pro 225	cgt Arg	gta Val	gcg Ala	caa Gln	ctc Leu 230	gca Ala	gaa Glu	aaa Lys	ttg Leu	cat His 235	cag Gln	aaa Lys	gcg Ala	cag Gln	gcc Ala 240		720
ggt Gly	gaa Glu	cga Arg	atg Met	cct Pro 245	Ser	tgc Cys	att Ile	aac Asn	atc Ile 250	Ile	agc Ser	ggc Gly	ccc Pro	agt Ser 255	tca Ser		768
acg Thr	gcg Ala	gat Asp	att Ile 260	gag Glu	ctt Leu	atc Ile	aaa Lys	gtc Val 265	Val	gga Gly	gtt Val	cat His	ggc Gly 270	ccg Pro	gtg Val		816
aaa Lys	gcg Ala	gtg Val 275	tat Tyr	ctg Leu	att Ile	att Ile	gag Glu 280	Asp	tgt Cys	tga *		•					849

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tgt Cys	aat Asn	ctc Leu	aaa Lys 20	tgt Cys	gat Asp	tac Tyr	tgt Cys	ttt Phe 25	tac Tyr	ctt Leu	gaa Glu	aaa Lys	gag Glu 30	tcg Ser	cag Gln	96
ttt Phe	act Thr	cat His 35	gaa Glu	aaa Lys	tgg Trp	atg Met	gat Asp 40	gac Asp	agc Ser	act Thr	ctg Leu	aaa Lys 45	gag Glu	ttc Phe	atc Ile	144
aaa Lys	caa Gln 50	tat Tyr	atc Ile	gca Ala	gcg Ala	tct Ser 55	ggc Gly	aat Asn	cag Gln	gtc Val	tat Tyr 60	ttt Phe	acc Thr	tgg Trp	caa Gln	192
ggc Gly 65	ggt Gly	gaa Glu	ccc Pro	act Thr	ctg Leu 70	gct Ala	ggc Gly	ctg Leu	gat Asp	ttt Phe 75	ttc Phe	cgt Arg	aaa Lys	gtt Val	att Ile 80	240
cac His	tat Tyr	caa Gln	caa Gln	cgc Arg 85	tat Tyr	gca Ala	ggc Gly	caa Gln	aaa Lys 90	cgt Arg	att Ile	ttt Phe	aat Asn	gca Ala 95	tta Leu	288
caa Gln	acg Thr	aat Asn	ggc Gly 100	att Ile	tta Leu	ttg Leu	aat Asn	aat Asn 105	gaa Glu	tgg Trp	tgt Cys	gcc Ala	ttt Phe 110	ctc Leu	aaa Lys	336
gaa Glu	cat His	gaa Glu 115	ttt Phe	ctg Leu	gtt Val	ggt Gly	atc Ile 120	tcg Ser	atc Ile	gat Asp	ggc Gly	ccc Pro 125	cag Gln	gag Glu	tta Leu	384
cat His	gac Asp 130	cgt Arg	tac Tyr	aga Arg	cgc Arg	agt Ser 135	aat Asn	tca Ser	ggt Gly	aac Asn	ggt Gly 140	act Thr	ttt Phe	gca Ala	aaa Lys	432
gtg Val 145	Ile	gca Ala	gcc Ala	atc Ile	gag Glu 150	cgt Arg	ctg Leu	aaa Lys	tca Ser	tat Tyr 155	caa Gln	gta Val	gag Glu	ttt Phe	aat Asn 160	480
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ttg Leu	cta Leu	gaa Glu 195	Thr	ggg	acg Thr	ccg Pro	aat Asn 200	att Ile	gat Asp	ttc Phe	agt Ser	ggt Gly 205	cat His	agt Ser	gag Glu	624

aac Asn	aca Thr 210	ttc Phe	cgt Arg	atc Ile	att Ile	gat Asp 215	ttt Phe	tct Ser	gtg Val	cct Pro	ccc Pro 220	acg Thr	gct Ala	tat Tyr	ggc Gly	672
aag Lys 225	ttt Phe	atg Met	tca Ser	acc Thr	att Ile 230	ttt Phe	atg Met	caa Gln	tgg Trp	gtt Val 235	aaa Lys	aac Asn	gat Asp	gtg Val	ggt Gly 240	720
gaa Glu	att Ile	ttc Phe	atc Ile	cgt Arg 245	cag Gln	ttt Phe	gaa Glu	agc Ser	ttt Phe 250	gtc Val	agc Ser	cgt Arg	ttt Phe	ttg Leu 255	GJ À dad	768
aat Asn	ggg ggg	cat His	acc Thr 260	agt Ser	tgt Cys	att Ile	ttc Phe	cag Gln 265	gag Glu	tcc Ser	tgc Cys	aag Lys	gat Asp 270	aat Asn	ctg Leu	816
gtt Val	gtt Val	gaa Glu 275	agt Ser	aat Asn	gga Gly	gac Asp	att Ile 280	tac Tyr	gaa Glu	tgc Cys	gac Asp	cat His 285	ttt Phe	gtc Val	tat Tyr	864
cca Pro	cag Gln 290	tac Tyr	aaa Lys	att Ile	gga Gly	aac Asn 295	att Ile	aat Asn	aaa Lys	tct Ser	gaa Glu 300	ctc Leu	aaa Lys	acg Thr	atg Met	912
aac Asn 305	agt Ser	gta Val	caa Gln	ctg Leu	aca Thr 310	gcg Ala	caa Gln	aaa Lys	aaa Lys	cgg Arg 315	att Ile	cca Pro	gcg Ala	aaa Lys	tgt Cys 320	960
cag Gln	caa Gln	tgt Cys	gca Ala	tat Tyr 325	aaa Lys	cct Pro	atc Ile	tgc Cys	aat Asn 330	ggc Gly	ggt Gly	tgt Cys	cct Pro	aag Lys 335	cat His	1008
cgt Arg	att Ile	act Thr	aaa Lys 340	gta Val	aac Asn	aat Asn	gag Glu	act Thr 345	gtt Val	tct Ser	tat Tyr	ttt Phe	tgc Cys 350	gaa Glu	ggt Gly	1056
tat Tyr	aaa Lys	atc Ile 355	ctt Leu	ttt Phe	tca Ser	acc Thr	aťg Met 360	gta Val	cct Pro	tat Tyr	atg Met	aac Asn 365	gcc Ala	atg Met	gta Val	1104
gag Glu	tta Leu 370	Ala	aag Lys	aac Asn	aga Arg	gta Val 375	ccg Pro	ctt Leu	tac Tyr	cac His	att Ile 380	Met	gat Asp	gtt Val	gca Ala	1152
	Gln			aat Asn		*										1173
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aag Lys	aaa Lys	agt Ser	gtc Val 20	gta Val	agt Ser	acc Thr	tcg Ser	ata Ile 25	tct Ser	ttg Leu	ata Ile	ctg Leu	gca Ala 30	tct Ser	ggt Gly		96
atg Met	gct Ala	gca Ala 35	ttt Phe	gct Ala	gct Ala	cat His	gcg Ala 40	gca Ala	gat Asp	gat Asp	gta Val	aag Lys 45	ctg Leu	aaa Lys	gca Ala	1	44
acc Thr	aaa Lys 50	aca Thr	aac Asn	gtt Val	gct Ala	ttc Phe 55	tca Ser	gac Asp	ttt Phe	acg Thr	ccg Pro 60	aca Thr	gaa Glu	tac Tyr	agt Ser	1	.92
acc Thr 65	aaa Lys	gga Gly	aag Lys	cca Pro	aat Asn 70	att Ile	atc Ile	gta Val	ctg Leu	acc Thr 75	atg Met	gat Asp	gat Asp	ctt Leu	ggt Gly 80	2	240
tat Tyr	gga Gly	caa Gln	ctt Leu	cct Pro 85	ttt Phe	gat Asp	aag Lys	gga Gly	tct Ser 90	ttt Phe	gac Asp	cca Pro	aaa Lys	aca Thr 95	atg Met	2	88
gaa Glu	aat Asn	cgt Arg	gaa Glu 100	gtt Val	gtc Val	gat Asp	acc Thr	tac Tyr 105	aaa Lys	ata Ile	ggg Gly	ata Ile	gat Asp 110	aaa Lys	gcc Ala	3	336
att Ile	gaa Glu	gct Ala 115	gca Ala	caa Gln	aaa Lys	tca Ser	acg Thr 120	ccg Pro	acg Thr	ctc Leu	ctt Leu	tca Ser 125	tta Leu	atg Met	gat Asp	3	384
gaa Glu	ggc Gly 130	gta Val	cgt Arg	ttt Phe	act Thr	aac Asn 135	ggc	tat Tyr	gtg Val	gca Ala	cac His 140	ggt Gly	gtt Val	tcc Ser	ggc	4	132
Pro 145	Ser	Arg	gcc Ala	Ala	Ile 150	Met	Thr	Gly	Arg	Ala 155	Pro	Ala	Arg	Phe	Gly 160	4	180
gtc Va l	tat Tyr	tcc Ser	aat Asn	acc Thr 165	gat Asp	gct Ala	cag Gln	gat Asp	ggt Gly 170	att Ile	ccg Pro	cta Leu	aca Thr	gaa Glu 175	act Thr	į	528
Phe	Leu	Pro	gaa Glu 180	Leu	Phe	Gln	Asn	His 185	Gly	Tyr	Tyr	Thr	Ala 190	Ala	Val	Ş	576
ggt Gly	aaa Lys	tgg Trp 195	cac His	ttg Leu	tca Ser	aaa Lys	atc Ile 200	Ser	aat Asn	gtg Val	ccg Pro	gta Val 205	Pro	gaa Glu	gat Asp	(624
aaa Lys	caa Gln 210	Thr	cgt Arg	gac Asp	tat Tyr	cat His 215	Asp	aac Asn	ttc Phe	acc Thr	Thr 220	Phe	tct Ser	gcg Ala	gaa Glu	(672
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gaa Glu	cgt Arg	gtc Val	ccc Pro 260	gca Ala	aaa Lys	ggt Gly	tat Tyr	atc Ile 265	agc Ser	gat Asp	cag Gln	tta Leu	acc Thr 270	gat Asp	gag Glu		816
gca Ala	att Ile	ggc Gly 275	gtt Val	gtt Val	gat Asp	cgt Arg	gcc Ala 280	aaa Lys	aca Thr	ctt Leu	gac Asp	cag Gln 285	cct Pro	ttt Phe	atg Met		864
ctt Leu	tac Tyr 290	ctg Leu	gct Ala	tat Tyr	aat Asn	gct Ala 295	ccg Pro	cac His	ctg Leu	cca Pro	aat Asn 300	gat Asp	aat Asn	cct Pro	gca Ala		912
ccg Pro 305	gat Asp	caa Gln	tat Tyr	cag Gln	aag Lys 310	caa Gln	ttt Phe	aat Asn	acc Thr	ggt Gly 315	agt Ser	caa Gln	aca Thr	gca Ala	gat Asp 320		960
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													att Ile 350				1056
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Gly	gcg Ala 370	caa Gln	aaa Lys	ggc Gly	tat Tyr	aag Lys 375	agt Ser	cag Gln	acc Thr	tat Tyr	cct Pro 380	ggc Gly	ggt Gly	act Thr	cac His		1152
acc Thr 385	cca Pro	atg Met	ttt Phe	atg Met	tgg Trp 390	tgg Trp	aaa Lys	gga Gly	aaa Lys	ctt Leu 395	caa Gln	ccc Pro	ggt Gly	aat Asn	tat Tyr 400		1200
gac Asp	aag Lys	ctg Leu	att Ile	tcc Ser 405	gca Ala	atg Met	gat Asp	ttc Phe	tac Tyr 410	ccg Pro	aca Thr	gct Ala	ctt Leu	gat Asp 415	gca Ala		1248 .
gcc Ala	gat Asp	atc Ile	agc Ser 420	att Ile	cca Pro	aaa Lys	gac Asp	ctt Leu 425	aag Lys	ctg Leu	gat Asp	ggc Gly	gtt Val 430	tcc Ser	ttg Leu		
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acc Thr	tgg Trp 450	Ile	acc Thr	tct Ser	tat Tyr	tct Ser 455	cac His	tgg Trp	ttt Phe	gac Asp	gag Glu 460	gaa Glu	aat Asn	att Ile	cca Pro	٠	1392 ·
ttc Phe 465	Trp	gat Asp	aat Asn	tac Tyr	cac His 470	aaa Lys	ttt Phe	gtt Val	cgc Arg	cat His 475	cag Gln	tca Ser	gac Asp	gat Asp	tac Tyr 480		1440

ccg cat aac Pro His Asn						_					-		1488
aga aat aac Arg Asn Asn													1536
ggt ctc tac Gly Leu Tyr 515													1584
gcc aat ccg Ala Asn Pro 530		_			_				_	_			1632
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Ile Ile Ile	Ser Thr	Ala Phe	Trp	Met 105	Phe	Trp	Arg	Thr	Trp 110	Arg	Gly		
gaa cgc aac Glu Arg Asr 115	Trp Leu	gag aat Glu Asr	atg Met 120	cac His	ggg Gly	cat His	gat Asp	tat Tyr 125	gag Glu	cat His	cat His	;	384
cat cac gat His His Asp 130	cac gaa His Glu	cat cac His His 135	His	gac Asp	cat His	gga Gly	cat His 140	cat His	cac His	cat His	cac His		432
gaa cat ggo Glu His Gly 145													480
att aaa cga Ile Lys Arc		Asp Gly										!	528
tta ttt ggd Leu Phe Gly	tta acc Leu Thr 180	ggt ggd Gly Gly	ctt Leu	atc Ile 185	ccc Pro	tgc Cys	ccg Pro	gca Ala	gca Ala 190	att Ile	acc Thr	!	576
gtg ctg ttg Val Leu Leu 195	lle Cys	att cac Ile Glr	ttg Leu 200	aaa Lys	gcc Ala	ctg Leu	aca Thr	ctg Leu 205	ggc Gly	gca Ala	aca Thr	:	624
ctg gtc gtc Leu Val Val 210	agt tto Ser Phe	agc att Ser Ile 215	: Gly	ctg Leu	gcg Ala	tta Leu	acg Thr 220	ctt Leu	gtc Val	acc Thr	gta Val		672
ggc gtt ggc Gly Val Gly 225	gca gca Ala Ala	atc ago Ile Sei 230	gtt Val	cag Gln	cag Gln	gtc Val 235	gca Ala	aaa Lys	cgc Arg	tgg Trp	agc Ser 240		720
gga ttt aad Gly Phe Asr	act cto Thr Leu 245	Ala Lys	cgc Arg	gcc Ala	ccc Pro 250	tat Tyr	ttt Phe	tcc Ser	agt Ser	ctg Leu 255	ttg Leu		768
att ggc tta Ile Gly Leu	gtc ggt Val Gly 260	gtg tat Val Ty	atg Met	ggc Gly 265	gta Val	cat His	ggc Gly	ttc Phe	atg Met 270	ggc Gly	ata Ile	1	816
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1				5					10				•	15		
				tcc Ser												96
				tcg Ser												144
		-		aca Thr	-			_		_		_				192
				ctg Leu												240
				acc Thr 85												288
				agt Ser												336
				gaa Glu												384
				aac Asn												432
tat Tyr 145	atg Met	ggt Gly	ggc Gly	gcg Ala	tac Tyr 150	gtg Val	ttg Leu	atc Ile	agc Ser	gac Asp 155	acc Thr	gac Asp	ggt Gly	aaa Lys	atc Ile 160	480
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				acg Thr												96

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					tat Tyr											192
caa Gln 65	ttt Phe	tat Tyr	ttt Phe	tca Ser	ctg Leu 70	gaa Glu	acc Thr	gca Ala	tgg Trp	tac Tyr 75	ctc Leu	ata Ile	tct Ser	gct Ala	gtt Val 80	240
gca Ala	gta Val	ttt Phe	att Ile	gca Ala 85	tct Șer	gtt Val	ttt Phe	ata Ile	cag Gln 90	cat His	aga Arg	att Ile	aaa Lys	gct Ala 95	tat Tyr	288
tta Leu	aca Thr	tta Leu	tta Leu 100	gct Ala	att Ile	aca Thr	tgg Trp	att Ile 105	gta Val	cta Leu	aca Thr	ata Ile	aca Thr 110	gat Asp	gtg Val	336
gcg Ala	tta Leu	ata Ile 115	cac His	gcc Ala	tta Leu	gac Asp	aat Asn 120	ata Tle	gcc Ala	atg Meț	aat Asn	aat Asn 125	att Ile	ttg Leu	tta Leu	384
aat Asn	ata Ile 130	cta Leu	tat Tyr	aat Asn	ctt Leu	ttt Phe 135	GJ Y ggg	gcg Ala	att Ile	tta Leu	ttg Leu 140	tca Ser	ctg Leu	ttt Phe	atg Met	432
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					gca Ala											528
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gta Val	gag Glu	att Ile 195	gag Glu	atg Met	gat Asp	ata Ile	tct Ser 200	gaa Glu	ggt Gly	tca Ser	gac Asp	atc Ile 205	gca Ala	tat Tyr	gta Val	624
					gag Glu											672
aca Thr 225	gac Asp	aca Thr	cca Pro	acg Thr	tat Tyr 230	ctg Leu	gat Asp	gta Val	atc Ile	aaa Lys 235	aat Asn	ggt Gly	agt Ser	ttg Leu	ata Ile 240	720
tat Tyr	aat Asn	gat Asp	aca Thr	cag Gln 245	ggt Gly	tta Leu	agt Ser	ggt Gly	gct Ala 250	gat Asp	att Ile	tat Tyr	att Ile	gtc Val 255	tcc Ser	768
					cca Pro											816

aaa Lys	aaa Lys	tct Ser 275	ttt Phe	ctg Leu	aat Asn	gta Val	aaa Lys 280	aag Lys	cta Leu	gaa Glu	atc Ile	aca Thr 285	cag Gln	aaa Lys	ctt Leu	864	
cca Pro	atg Met 290	atg Met	ggg Gly	ttc Phe	ata Ile	caa Gln 295	ggt Gly	gaa Glu	tcc Ser	gct Ala	gat Asp 300	gtg Val	atg Met	cct Pro	aaa Lys	912	
gca Ala 305	gca Ala	tcc Ser	agg Arg	tta Leu	agt Ser 310	ttg Leu	agc Ser	aag Lys	caa Gln	gat Asp 315	gat Asp	aaa Lys	ttt Phe	atg Met	cta Leu 320	960)
gcc Ala	tca Ser	agt Ser	gtt Val	act Thr 325	gac Asp	tct Ser	caa Gln	ata Ile	aaa Lys 330	ttt Phe	aaa Lys	tca Ser	aac Asn	aat Asn 335	gca Ala	. 1008	}
caa Gln	ttg Leu	atg Met	gtt Val 340	gct Ala	ttc Phe	gca Ala	ttt Phe	atg Met 345	cca Pro	ata Ile	aca Thr	acg Thr	aat Asn 350	ggt Gly	att Ile	1056	5
tta Leu	cat His	gat Asp 355	tat Tyr	aca Thr	tac Tyr	gat Asp	ata Ile 360	ata Ile	ata Ile	aat Asn	gat Asp	aaa Lys 365	aaa Lys	tat Tyr	aaa Lys	1104	l
att Ile	gaa Glu 370	aat Asn	cat His	gtt Val	gca Ala	cct Pro 375	cta Leu	tct Ser	agg Arg	ctt Leu	gat Asp 380	aaa Lys	aat Asn	aag Lys	aag Lys	1152	?
atg Met 385	aag Lys	tgt Cys	gaa Glu	tac Tyr	cag Gln 390	caa Gln	ata Ile	tcg Ser	gat Asp	tta Leu 395	aca Thr	aat Asn	acg Thr	tat Tyr	aac Asn 400	1200)
att Ile	aat Asn	gca Ala	aat Asn	tac Tyr 405	tta Leu	acg Thr	ggt Gly	ttt Phe	tta Leu 410	ctt Leu	gtc Val	cta Leu	aaa Lys	cca Pro 415	gat Asp	1248	3
gat Asp	att Ile	att Ile	aat Asn 420	tac Tyr	aac Asn	aat Asn	agc Ser	cct Pro 425	tcc Ser	gta Val	cta Leu	ctc Leu	aag Lys 430	act Thr	gat Asp	1296	5
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cag Gln 465	Phe	agt Ser	atc Ile	aac Asn	ggg Gly 470	aaa Lys	cat His	ttg Leu	tcg Ser	tta Leu 475	agg Arg	cca Pro	gaa Glu	tcg Ser	gag Glu 480	1440	0
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aaa Lys	atc Ile	aaa Lys	ata Ile 500	tat Tyr	ggc	aca Thr	gca Ala	gat Asp 505	Leu	gtt Val	ttt Phe	gtt Val	gat Asp 510	Asn	aag Lys	153	6

ata atg aac ctt Ile Met Asn Leu 515	cgt aaa ata Arg Lys Ile	act tat tto Thr Tyr Lev 520	g caa tot aag o u Gln Ser Lys L 525	eta gaa att 1584 eu Glu Ile	
ttt ggt tct tct Phe Gly Ser Ser 530	att atg gat Ile Met Asp 535	Ile Leu Ly:	g tat ata ttt g s Tyr Ile Phe G 540	gt tta ggt 1632 ly Leu Gly	
ctg cta gca att Leu Leu Ala Ile 545	tct ata aaa Ser Ile Lys 550	ttc att cat Phe Ile His	t tct tac ttt a s Ser Tyr Phe I 555	ag aat gat 1680 Lys Asn Asp 560	
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ggc aaa aga cg Gly Lys Arg Ar 35	a gta aga att g Val Arg Ile	tca agt ca Ser Ser Gl 40	a agc ctt aaa o n Ser Leu Lys <i>l</i> 45	egt geg atg 144 Arg Ala Met	
cgt aaa agt gg Arg Lys Ser Gl 50	t tat tac goa y Tyr Tyr Ala 55	Gln Asn Il	t ggt gaa too a e Gly Glu Ser 9 60	agt ctc aga 192 Ger Leu Arg	
acc att cat ct Thr Ile His Le 65	t gca caa tta u Ala Gln Lev 70	a cgt gat gt n Arg Asp Va	t ctt cgg caa a l Leu Arg Gln l 75	aaa ctt ggt 240 Lys Leu Gly 80	
gaa cgt ttt ga Glu Arg Phe As	c caa aaa ato o Gln Lys Ile 85	e atc gat aa e Ile Asp Ly 9	s Thr Leu Ala 1	ctg ctc tcc 288 Leu Leu Ser 95	
ggt aaa tca gt Gly Lys Ser Va 10	l Asp Glu Ala	gaa aag at Glu Lys Il 105	e Ser Ala Asp	gcg gtt act 336 Ala Val Thr 110	;
ccc tgg gtt gt Pro Trp Val Va 115	l Gly Glu Ile	a gcc tgg tt e Ala Trp Ph 120	c tgt gag cag o e Cys Glu Gln ' 125	gtt gca aaa 384 Val Ala Lys	•

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gaa Glu 145	gat Asp	att Ile	gcc Ala	gcc Ala	ata Ile 150	cgt Arg	gtg Val	aat Asn	tta Leu	cag Gln 155	cag Gln	ggt Gly	gtt Val	gat Asp	att Ile 160	480
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tct Ser	atg Met 290	gca Ala	aat Asn	gct Ala	ttt Phe	gaa Glu 295	aaa Lys	gcg Ala	gtt Val	aaa Lys	gcg Ala 300	aaa Lys	gat Asp	ggc Gly	ttt Phe	912
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aat Asn	gga Gly	tat Tyr	ggt Gly	ctg Leu 325	Asn	gga Gly	gct Ala	gct Ala	gcg Ala 330	caa Gln	ttc Phe	agc Ser	tta Leu	tct Ser 335	gat Asp	1008
gta Val	gac Asp	cca Pro	att Ile 340	act Thr	gct Ala	caa Gln	gtt Val	aaa Lys 345	caa Gln	atg Met	cct Pro	act Thr	tta Leu 350	Glu	cag Gln	1056
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Arg Leu Pro His Val Pro Glu Gly His Lys Cys Gly Arg Leu His Gly
             20
cat tcc ttt atg gtg cga ctg gaa att acc ggg gaa gtc gat ccg cat
                                                                      144
His Ser Phe Met Val Arg Leu Glu Ile Thr Gly Glu Val Asp Pro His
acg ggc tgg att atc gat ttc gct gaa cta aaa gcg gcg ttt aaa cca
                                                                      192
Thr Gly Trp Ile Ile Asp Phe Ala Glu Leu Lys Ala Ala Phe Lys Pro
     50
                         55
acc tac gag cgc ctc gat cac cat tat ctc aat gat att cca ggt ctg
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Thr Tyr Glu Arg Leu Asp His His Tyr Leu Asn Asp Ile Pro Gly Leu
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qaa aac cca acc agc qag gtt tta gca aaa tgg att tgg gat cag gtt
Glu Asn Pro Thr Ser Glu Val Leu Ala Lys Trp Ile Trp Asp Gln Val
                 85
aaa ccc gtt gtg ccg ctg tta agt gcg gtg atg gta aaa gaa acc tgc
                                                                      336
Lys Pro Val Val Pro Leu Leu Ser Ala Val Met Val Lys Glu Thr Cys .
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Ile Ile Ile Ile Gly Ala Gly Ile Ala Gly Thr Ala Cys Ala Leu Arg
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ggc atg gat a Gly Met Asp N	atg gcg ctg Met Ala Leu 325	act ggc gcg Thr Gly Ala	cag gcg gcg gca Gln Ala Ala Ala 330	caa acg ctg 1008 Gln Thr Leu 335
Ile Ser Ala (tgc cag cac Cys Gln His 340	cgc gag ccg Arg Glu Pro 345	caa aat ctg ttt Gln Asn Leu Phe	ccg ctt tat 1056 Pro Leu Tyr 350
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cag cat gtt o Gln His Val 1 370	ccg gcg ctt Pro Ala Leu	ttg caa cgc Leu Gln Arg 375	ccg gga tgg tac Pro Gly Trp Tyr 380	cgt acg tgg 1152 Arg Thr Trp
cct gcg tta a Pro Ala Leu l 385	atg cag gat Met Gln Asp 390	att tcc cgc Ile Ser Arg	gat tta tgg gat Asp Leu Trp Asp 395	cag ggt gat 1200 Gln Gly Asp 400
aaa cct gtt (Lys Pro Val	cca ccg ctg Pro Pro Leu 405	cgc cag tta Arg Gln Leu	ttc tgg cat cat Phe Trp His His 410	tta cgt cgt 1248 Leu Arg Arg 415
His Gly Leu	tgg cat ctg Trp His Leu 420	gcg ggc gat Ala Gly Asp 425	gtt atc agg agt Val Ile Arg Ser	ctg cga tgt 1296 Leu Arg Cys 430
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ggt ctt ttt tcg ctc aca ccg gaa ggt aac tta cgt att gac tat cgc Gly Leu Phe Ser Leu Thr Pro Glu Gly Asn Leu Arg Ile Asp Tyr Arg 50 55 60	192
agt tgc ctg gag tgt ggc acc tgc cgt ttg ctg tgc gac gaa tca aca Ser Cys Leu Glu Cys Gly Thr Cys Arg Leu Leu Cys Asp Glu Ser Thr 65 70 75 80	240
cta caa cag tgg cgc tat ccg cct tcc gga ttc ggc atc acc tac cgc Leu Gln Gln Trp Arg Tyr Pro Pro Ser Gly Phe Gly Ile Thr Tyr Arg 85 90 95	288
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tca att tcg ttt cac aac att gat aag caa gtt gcg caa tcg aat ccg Ser Ile Ser Phe His Asn Ile Asp Lys Gln Val Ala Gln Ser Asn Pro 115 120 125	384
gat tgt att gag atc ctg cca ggc tgt atg ccc aaa gtg ctg ggc tgg Asp Cys Ile Glu Ile Leu Pro Gly Cys Met Pro Lys Val Leu Gly Trp 130 135 140	432
gtg aca gag aaa atc cgc caa ccg ctg att gcc ggt ggg ctg gtg tgc Val Thr Glu Lys Ile Arg Gln Pro Leu Ile Ala Gly Gly Leu Val Cys 145 150 155	480
gat gaa gaa gat gcg cgt aat gcg att aac gcg ggt gtc gtg gcg ctt Asp Glu Glu Asp Ala Arg Asn Ala Ile Asn Ala Gly Val Val Ala Leu 165 170 175	528
tee ace acg aat ace ggg gte tgg acg tta geg aaa aaa tta ett tga Ser Thr Thr Asn Thr Gly Val Trp Thr Leu Ala Lys Lys Leu Leu * 180 185 190	576
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	ggc Gly 130		_	_	_												405
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	act Thr																96
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	ctt Leu 50																192
	cag Gln																240
	gat Asp																288
	aac Asn																336
·cag Gln	gca Ala																384
	aaa Lys 130																432
	caa Gln																480

145	150	155	160
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ctt ggg caa acc gcc Leu Gly Gln Thr Ala 180	acc tct ggc att Thr Ser Gly Ile 185	gtt tcc gca tta ggc Val Ser Ala Leu Gly 190	cgc agc 576 Arg Ser
ggg ttg aat ctt gaa Gly Leu Asn Leu Glu 195	ggt ctg gaa aac Gly Leu Glu Asn 200	ttt atc cag aca gat Phe Ile Gln Thr Asp 205	gct tcc 624 Ala Ser
att aac cgc ggt aac Ile Asn Arg Gly Asn 210	tcc ggc ggt gca Ser Gly Gly Ala 215	cta tta aac ctt aac Leu Leu Asn Leu Asn 220	ggt gag 672 Gly Glu
tta att ggc atc aac Leu Ile Gly Ile Asn 225	act gca atc ctt Thr Ala Ile Leu 230	gcg cct ggc ggc ggg Ala Pro Gly Gly Gly 235	agc gtc 720 Ser Val 240
ggg att gga ttt gcc Gly Ile Gly Phe Ala 245	Ile Pro Ser Asn	atg gcg cga aca ctg Met Ala Arg Thr Leu 250	gcg cag 768 Ala Gln 255
cag ctt atc gac ttt Gln Leu Ile Asp Phe 260	ggt gaa atc aaa Gly Glu Ile Lys 265	cgc ggt ttg tta ggc Arg Gly Leu Leu Gly 270	atc aaa 816 Ile Lys
ggc acc gag atg agt Gly Thr Glu Met Ser 275	gcc gat atc gcc Ala Asp Ile Ala 280	aaa gcc ttc aac ctt Lys Ala Phe Asn Leu 285	gac gtg 864 Asp Val
cag cgt ggc gcg ttt Gln Arg Gly Ala Phe 290	gtc agc gaa gtg Val Ser Glu Val 295	ttg cca ggt tct ggc Leu Pro Gly Ser Gly 300	tcg gca 912 Ser Ala
aaa gcg ggc gtc aaa Lys Ala Gly Val Lys 305	gcg ggc gat att Ala Gly Asp Ile 310	att acc agc ctc aac Ile Thr Ser Leu Asn 315	ggc aaa 960 Gly Lys 320
ccg ctg aat agc ttt Pro Leu Asn Ser Phe 325	Ala Glu Leu Arg	tct cgt atc gcg acc Ser Arg Ile Ala Thr 330	acc gag 1008 Thr Glu 335
ccg ggc acg aaa gto Pro Gly Thr Lys Val 340	g aag ctt ggc ctg Lys Leu Gly Leu 345	ctg cgt aac ggc aaa Leu Arg Asn Gly Lys 350	cca ctg 1056 Pro Leu
gaa gta gaa gtg acq Glu Val Glu Val Thi 355	g ctc gat acc agc r Leu Asp Thr Ser 360	acc tct tcg tcg gcc Thr Ser Ser Ser Ala 365	agc gct 1104 Ser Ala
gaa atg atc acg cca Glu Met Ile Thr Pro 370	a gcg ctg gaa ggt o Ala Leu Glu Gly 375	gca acg ttg agc gat Ala Thr Leu Ser Asp 380	ggt cag 1152 Gly Gln
cta aaa gat ggc ggo Leu Lys Asp Gly Gly	c aaa ggt att aaa y Lys Gly Ile Lys	atc gat gaa gtt gtc Ile Asp Glu Val Val	aaa gga 1200 Lys Gly

385	390	395	400
agc cca gct gct cag Ser Pro Ala Ala Gln 405	gct ggc ttg caa aaa Ala Gly Leu Gln Lys 410	gac gat gtg atc att Asp Asp Val Ile Ile 415	Gly
gtc aac cgc gat cgg Val Asn Arg Asp Arg 420	gtg aac tcg att gct Val Asn Ser Ile Ala 425	gaa atg cgt aaa gtg Glu Met Arg Lys Val 430	ctg 1296 Leu
gcg gca aaa ccg gcc Ala Ala Lys Pro Ala 435	atc atc gcc ctg caa Ile Ile Ala Leu Gln 440	att gta cgc ggc aat Ile Val Arg Gly Asn 445	gaa 1344 Glu
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	gcc gcg cca gcg gtg Ala Ala Pro Ala Val 55	=	
	tct cac aac cag ctt Ser His Asn Gln Leu 70		
22 2	gat caa cgc ggt tat Asp Gln Arg Gly Tyr 90	Ile Ile Thr Asn Lys	His
gtc atc aac gac gcc Val Ile Asn Asp Ala 100	gat cag atc atc gtc Asp Gln Ile Ile Val 105	gcc tta cag gat gga Ala Leu Gln Asp Gly 110	cgt 336 Arg
gta ttt gaa gca ttg Val Phe Glu Ala Leu 115	ctg gtg gga tct gac Leu Val Gly Ser Asp 120	tct cta acc gat cto Ser Leu Thr Asp Leu 125	g gcg 384 i Ala

gta Val	ctt Leu 130	aaa Lys	att Ile	aat Asn	gcc Ala	act Thr 135	ggc Gly	ggt Gly	tta Leu	cct Pro	acc Thr 140	att Ile	cca Pro	att Ile	aat Asn	432
gca Ala 145	cgt Arg	cgc Arg	gta Val	ccg Pro	cac His 150	att Ile	ggc Gly	gac Asp	gta Val	gta Val 155	ctg Leu	gcg Ala	atc Ile	ggt Gly	aac Asn 160	480
ccg Pro	tac Tyr	aac Asn	ctc Leu	ggg Gly 165	cag Gln	acc Thr	att Ile	acc Thr	cag Gln 170	ggg Gly	att Ile	att Ile	agt Ser	gcc Ala 175	acg Thr	528
ggt Gly	cga Arg	atc Ile	ggt Gly 180	ctg Leu	aac Asn	ccg Pro	acc Thr	ggg Gly 185	cgg Arg	caa Gln	aac Asn	ttc Phe	ctc Leu 190	caa Gln	acc Thr	576
gat Asp	gct Ala	tcc Ser 195	att Ile	aac Asn	cac His	ggt Gly	aac Asn 200	tct Ser	ggc Gly	ggc Gly	gcg Ala	ctg Leu 205	gtg Val	aac Asn	tcg Ser	624
ctg Leu	ggc Gly 210	gaa Glu	ctg Leu	atg Met	ggc Gly	att Ile 215	aat Asn	acg Thr	ctg Leu	tcg Ser	ttt Phe 220	gat Asp	aag Lys	agt Ser	aac Asn	672
gat Asp 225	ggc Gly	gaa Glu	acg Thr	ccg Pro	gaa Glu 230	ggt Gly	atc Ile	ggc	ttt Phe	gcg Ala 235	att Ile	cct Pro	ttc Phe	cag Gln	tta Leu 240	720
gca Ala	acc Thr	aaa Lys	att Ile	atg Met 245	gat Asp	aag Lys	ctg Leu	atc Ile	cgc Arg 250	gat Asp	ggt Gly	cgc Arg	gtg Val	atc Ile 255	cgc Arg	768
ggc Gly	tac Tyr	att Ile	ggt Gly 260	atc Ile	ggc Gly	gga Gly	cgt Arg	gag Glu 265	atc Ile	gca Ala	cca Pro	ctg Leu	cac His 270	gcg Ala	cag Gln	816
ggc Gly	ggt Gly	ggt Gly 275	ata Ile	gat Asp	caa Gln	ctg Leu	caa Gln 280	GJA	atc Ile	gtg Val	gtt Val	aat Asn 285	gaa Glu	gtg Val	tca Ser	864
cct Pro	gac Asp 290	ggc Gly	ccg Pro	gcg Ala	gcg Ala	aat Asn 295	gcg Ala	ggt Gly	att Ile	cag Gln	gtc Val 300	aac Asn	gat Asp	ctg Leu	att Ile	912
att Ile 305	tcg Ser	gtg Val	gat Asp	aac Asn	aaa Lys 310	ccg Pro	gcc Ala	atc Ile	tct Ser	gct Ala 315	ctg Leu	gag Glu	acg Thr	atg Met	gat Asp 320	960
cag Gln	gtg Val	gcg Ala	gaa Glu	att Ile 325	cgc Arg	cct Pro	ggt Gly	tcg Ser	gtg Val 330	Ile	cct Pro	gta Val	gta Val	gtg Val 335	Met	1008
cgt Arg	gat Asp	gat Asp	aag Lys 340	Gln	tta Leu	acg Thr	ctg Leu	cag Gln 345	Val	acc . Thr	att Ile	cag Gln	gaa Glu 350	Tyr	ccg Pro	1056
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atc ctg gct gca gcg g Ile Leu Ala Ala Ala G 35	ggt atc gct Gly Ile Ala 40	gaa gat gtt a Glu Asp Val 1	aag atc agt gag Lys Ile Ser Glu 45	ctg 144 Leu
tct gaa gga caa atc g Ser Glu Gly Gln Ile A 50				
gtt gaa ggt gat ctg c Val Glu Gly Asp Leu A 65				
atg gat ctt ggt tgc t Met Asp Leu Gly Cys T 85				
gtt cgc ggt cag cgt a Val Arg Gly Gln Arg T 100				
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Ser	Asp	Gly	Val 20	Ala	His	Ile	His	Ala 25	Ser	Phe	Asn	Asn	Thr 30	Ile	Val	
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ggt Gly	tcc Ser 50	ggt Gly	ttc Phe	cgt Arg	ggt Gly	tct Ser 55	cgc Arg	aaa Lys	tcc Ser	act Thr	ccg Pro 60	ttt Phe	gca Ala	gct Ala	cag Gln	192
gtt Val 65	gca Ala	gca Ala	gag Glu	cgt Arg	tgc Cys 70	gct Ala	gac Asp	gcc Ala	gtg Val	aaa Lys 75	gaa Glu	tac Tyr	ggc	atc Ile	aag Lys 80	240
aat Asn	ctg Leu	gaa Glu	gtt Val	atg Met 85	gtt Val	aaa Lys	ggt Gly	ccg Pro	ggt Gly 90	cca Pro	ggc Gly	cgc Arg	gaa Glu	tct Ser 95	act Thr	288
att Ile	cgt Arg	gct Ala	ctg Leu 100	aac Asn	gcc Ala	gca Ala	ggt ['] Gly	ttc Phe 105	cgc Arg	atc Ile	act Thr	aac Asn	att Ile 110	act Thr	gat. Asp	336
gtg Val	act Thr	ccg Pro 115	atc Ile	cct Pro	cat His	aac Asn	ggt Gly 120	tgt Cys	cgt Arg	ccg Pro	ccg Pro	aaa Lys 125	aaa Lys	cgt Arg	cgc Arg	384
gta Val	taa *															390
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65					70					75					80	
	ctg Leu															288
	ctg Leu															336
	gca Ala															384
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	cgt Arg															480
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_	atg Met	_		_		_	-	-	_		-		_	_		576
	gac Asp													taa *		621
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	caa Gln															96
cgt Arg	ggc Gly	ttt Phe 35	ggc Gly	cat His	act Thr	ctg Leu	ggt Gly 40	aac Asn	gca Ala	ctg Leu	cgc Arg	cgt Arg 45	att Ile	ctg Leu	ctc Leu	144
	tcg Ser 50															192

cta Leu 65	cat His	gag Glu	tac Tyr	agc Ser	acc Thr 70	aaa Lys	gaa Glu	ggc Gly	gtt Val	cag Gln 75	gaa Glu	gat Asp	atc Ile	ctg Leu	gaa Glu 80	240
atc Ile	ctg Leu	ctc Leu	aac Asn	ctg Leu 85	aaa Lys	ggg Gly	ctg Leu	gcg Ala	gtg Val 90	aga Arg	gtt Val	cag Gln	ggc Gly	aaa Lys 95	gat Asp	288
gaa Glu	gtt Val	att Ile	ctt Leu 100	acc Thr	ttg Leu	aat Asn	aaa Lys	tct Ser 105	ggc Gly	att Ile	ggc Gly	cct Pro	gtg Val 110	act Thr	gca Ala	336
gcc Ala	gat Asp	atc Ile 115	acc Thr	cac His	gac Asp	ggt Gly	gat Asp 120	gtc Val	gaa Glu	atc Ile	gtc Val	aag Lys 125	ccg Pro	cag Gln	cac His	384
gtg Val	atc Ile 130	tgc Cys	cac His	ctg Leu	acc Thr	gat Asp 135	gag Glu	aac Asn	gcg Ala	tct Ser	att Ile 140	agc Ser	atg Met	cgt Arg	atc Ile	432
aaa Lys 145	gtt Val	cag Gln	cgc Arg	ggt Gly	cgt Arg 150	ggt Gly	tat Tyr	gtg Val	ccg Pro	gct Ala 155	tct Ser	acc Thr	cga Arg	att Ile	cat His 160	480
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tac Tyr	agc Ser	cct Pro	gtg Val 180	gag Glu	cgt Arg	att Ile	gcc Ala	tac Tyr 185	aat Asn	gtt Val	gaa Glu	gca Ala	gcg Ala 190	cgt Arg	gta Val	576
gaa Glu	cag Gln	cgt Arg 195	acc Thr	gac Asp	ctg Leu	gac Asp	aag Lys 200	ctg Leu	gtc Val	atc Ile	gaa Glu	atg Met 205	gaa Glu	acc Thr	aac Asn	624
ggc Gly	aca Thr 210	atc Ile	gat Asp	cct Pro	gaa Glu	gag Glu 215	gcg Ala	att Ile	cgt Arg	cgt Arg	gcg Ala 220	gca Ala	acc Thr	att Ile	ctg Leu	672
gct Ala 225	gaa Glu	caa Gln	ctg Leu	gaa Glu	gct Ala 230	ttc Phe	gtt Val	gac Asp	tta Leu	cgt Arg 235	gat Asp	gta Val	cgt Arg	cag Gln	cct Pro 240	720
gaa Glu	gtg Val	aaa Lys	gaa Glu	gag Glu 245	aaa Lys	cca Pro	gag Glu	ttc Phe	gat Asp 250	ccg Pro	atc Ile	ctg Leu	ctg Leu	cgc Arg 255	cct Pro	768
gtt Val	gac Asp	gat Asp	ctg Leu 260	gaa Glu	ttg Leu	act Thr	gtc Val	cgc Arg 265	tct Ser	gct Ala	aac Asn	tgc Cys	ctt Leu 270	aaa Lys	gca Ala	816
					atc Ile											864
ctc Leu	ctt Leu 290	aaa Lys	acg Thr	cct Pro	aac Asn	ctt Leu 295	ggt Gly	aaa Lys	aaa Lys	tct Ser	ctt Leu 300	Thr	gag Glu	att Ile	aaa Lys	912

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atc atc aag acg act ctg cct aaa gcg aaa gag ctg cgc cgc gta gtt Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val 35 40 45	144
gag ccg ctg att act ctt gcc aag act gat agc gtt gct aat cgt cgt Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg 50 55 60	192
ctg gca ttc gcc cgt act cgt gat aac gag atc gtg gca aaa ctg ttt Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe 65 70 75 80	240
aac gaa ctg ggc ccg cgt ttc gcg agc cgt gcc ggt ggt tac act cgt Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg 85 90 95	288
att ctg aag tgt ggc ttc cgt gca ggc gac aac gcg ccg atg gct tac Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr 100 105 110	336
atc gag ctg gtt gat cgt tca gag aaa gca gaa gct gct gca gag taa Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu * 115 120 125	384
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ggc ttc cgt Gly Phe Arg	gct cgt a Ala Arg M 20	atg gct a Met Ala T	act aaa Thr Lys 25	aat ggt Asn Gly	cgt cag Arg Gln	gtt ctg Val Leu 30	gca 96 Ala
cgt cgt cgt Arg Arg Arg 35	gct aaa (Ala Lys (ggc cgc g Gly Arg A	gct cgt Ala Arg 40	ctg acc Leu Thr	gtt tct Val Ser 45	aag taa Lys *	141
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caa ttc aca Gln Phe Thr							
att acc att Ile Thr Ile 35	ctc ggc (Leu Gly)	cgc ctg a Arg Leu A	aat tcg Asn Ser 40	ctg ggg Leu Gly	cat ccc His Pro 45	cgt atc Arg Ile	ggt 144 Gly
ctt aca gtc Leu Thr Val 50	gcc aag a Ala Lys :	aaa aac g Lys Asn V 55	gtt cga Val Arg	cgc gcc Arg Ala	cat gaa His Glu 60	cgc aat Arg Asn	cgg 192 Arg
att aaa cgt Ile Lys Arg 65	ctg acg	cgt gaa a Arg Glu S 70	agc ttc Ser Phe	cgt ctg Arg Leu 75	cgc caa Arg Gln	cat gaa His Glu	ctc 240 Leu 80
ccg gct atg Pro Ala Met	gat ttc Asp Phe	gtg gtg g Val Val V	gtg gcg Val Ala	aaa aaa Lys Lys 90	ggg gtt Gly Val	gcc gac Ala Asp 95	Leu
gat aac cgt Asp Asn Arg	gct ctc Ala Leu 100	tcg gaa g Ser Glu <i>F</i>	gcg ttg Ala Leu 105	gaa aaa Glu Lys	tta tgg Leu Trp	cgc cgc Arg Arg 110	cac 336 His
tgt cgc ctg Cys Arg Leu 115	-		tga *				360

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											gac Asp					144
											aac Asn 60					192
											ccg Pro					240
											gta Val					288
ctg Leu	gtg Val	gtt Val	gac Asp 100	gca Ala	ttt Phe	gac Asp	ggc Gly	ccg Pro 105	atg Met	ccg Pro	caa Gln	acg Thr	cgc Arg 110	ttc Phe	gta Val	336
											att Ile					384
	-	-	_				-		_		gtt Val 140		-	-	_	432
											gag Glu					480
ccg Pro	atc Ile	gtt Val	tac Tyr	gct Ala 165	tct Ser	gcg Ala	ctg Leu	aac Asn	ggt Gly 170	atc Ile	gcg Ala	ggt Gly	ctg Leu	gac Asp 175	cac His	528
											cag Gln					576
	-			_	_	-	_		_		ccg Pro		_	_	-	624

att Ile	tct Ser 210	cag Gln	ctc Leu	gat Asp	tac Tyr	aac Asn 215	agc Ser	tat Tyr	gtt Val	ggc Gly	gtt Val 220	atc Ile	ggc Gly	att Ile	ggc Gly	672
					aaa Lys 230											720
gat Asp	agc Ser	gaa Glu	ggc Gly	aaa Lys 245	acc Thr	cgc Arg	aac Asn	gcg Ala	aaa Lys 250	gtc Val	ggt Gly	aaa Lys	gtg Val	ctg Leu 255	ggc Gly	768
					cgt Arg											816
	-			_	ggc Gly			_	_				-		_	864
					gtt Val											912
					ttc Phe 310											960
					gta Val											1008
aaa Lys	gaa Glu	ctg Leu	gta Val 340	cac His	aac Asn	gtt Val	gcg Ala	ctg Leu 345	cgc Arg	gta Val	gaa Glu	gaa Glu	acc Thr 350	gaa Glu	gac Asp	1056
gcc Ala	gat Asp	gcg Ala 355	ttc Phe	cgc Arg	gtt Val	tct Ser	ggt Gly 360	cgt Arg	ggc Gly	gaa Glu	ctg Leu	cac His 365	ctg Leu	tct Ser	gtt Val	1104
					cgt Arg											1152
		_			cgt Arg 390	-		-		_				_		1200
gaa Glu	aac Asn	gtg Val	act Thr	ctg Leu 405	gac Asp	gtt Val	gaa Glu	gaa Glu	cag Gln 410	cat His	cag Gln	ggt Gly	tct Ser	gta Val 415	atg Met	1248
cag Gln	gcg Ala	ctg Leu	ggc Gly 420	gaa Glu	cgt Arg	aaa Lys	ggc Gly	gac Asp 425	ctg Leu	aaa Lys	aac Asn	atg Met	aat Asn 430	cca Pro	gac Asp	1296
ggt Gly	aaa Lys	ggc Gly 435	cgc Arg	gta Val	cgt Arg	ctc Leu	gac Asp 440	tac Tyr	gtg Val	atc Ile	cca Pro	agc Ser 445	cgt Arg	ggt Gly	ctg Leu	1344

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ctg tac tcc acc t Leu Tyr Ser Thr 1 465	-	Tyr Asp Asp	
ggt cag cgt cag a Gly Gln Arg Gln			
gtc gcg ttc gcg o Val Ala Phe Ala i 500			
ggt cac ggt gca o Gly His Gly Ala o 515			
cgc tct aac gac o Arg Ser Asn Asp 1 530			
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atc cgc atg act of the line arg Met Thr			
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			caa Gln														288
			gcc Ala 100														336
			att Ile														384
			atg Met														432
			atg Met														480
			cag Gln														528
			gac Asp 180														576
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ggc Gly	gaa Glu 210	agc Ser	gaa Glu	aaa Lys	tat Tyr	gcc Ala 215	gca Ala	cgc Arg	gta Val	ttt Phe	ggt Gly 220	gcc Ala	gat Asp	cgc Arg	tcc Ser		672
tgg Trp 225	tcg Ser	gta Val	gtc Val	gtc Val	ggt Gly 230	act Thr	tcc Ser	ggc Gly	tct Ser	aac Asn 235	cgc Arg	acc Thr	atc Ile	atg Met	cag Gln 240		720
gct Ala	tgc Cys	atg Met	acc Thr	gat Asp 245	aac Asn	gat Asp	gtc Val	gtg Val	gtc Val 250	gtt Val	gac Asp	cgt Arg	aac Asn	tgc Cys 255	cat His		768 :
			gaa Glu 260													-	816
atg Met	gtg Val	cca Pro 275	agc Ser	cgc Arg	aac Asn	cgc Arg	tac Tyr 280	ggc Gly	att Ile	atc Ile	ggg Gly	cca Pro 285	atc Ile	tat Tyr	ccg Pro		864

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	acc Thr														960
	tgc Cys		_			_			_		-		_	-	1008
	ctg Leu														1056
	tat Tyr														1104
	gaa Glu 370		 _						_		-				1152
	cac His														1200
	gaa Glu														1248
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-	gtg Val		 _	-	_	_			_		_		_		1344
_	gaa Glu 450		-	-		-	_		-	_		-			1392
	tat Tyr				-	_		_					_		1440
	aaa Lys														1488
	gac Asp														1536
	cat His														1584

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					cgc Arg											1728
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					acc Thr											1824
					cag Gln											1872
					atg Met 630											1920 .
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					gcg Ala											2016
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					tca Ser											2112
ctg Leu 705	ctg Leu	tct Ser	ggt Gly	gaa Glu	aac Asn 710	ttc Phe	ggc Gly	gat Asp	aaa Lys	aac Asn 715	agt Ser	ccg Pro	caa Gln	gta Val	agt Ser 720	2160
tat Tyr	tta Leu	cgc Arg	tcg Ser	ctg Leu 725	caa Gln	tcc Ser	tgg Trp	gac. Asp	cac His 730	cat His	ttc Phe	cct Pro	gga Gly	ttt Phe 735	gaa Glu	2208
cac His	gaa Glu	act Thr	gaa Glu 740	Gly	act Thr	gaa Glu	att Ile	att Ile 745	gac Asp	ggt Gly	att Ile	tac Tyr	cac His 750	gtt Val	atg Met	2256
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Ile Ile Thr Thr		Arg Tyr Ala Val 200	Asn Glu Leu Met 205	Met
gac ggt aaa aat Asp Gly Lys Asn 210	atc tct cag g Ile Ser Gln V 215	gta tca cag tcc Val Ser Gln Ser	tgc ggc tac aac Cys Gly Tyr Asn 220	agt 672 Ser
acg tcg tac ttt Thr Ser Tyr Phe 225	att tot gto t Ile Ser Val E 230	ttt aaa gac ttc Phe Lys Asp Phe 235	tac ggt atg acg Tyr Gly Met Thr	ccg 720 Pro 240
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caa cgg aaa gct Gln Arg Lys Ala 35				
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ctt ggc att acg Leu Gly Ile Thr 65	gat att cag o Asp Ile Gln <i>F</i> 70	gct act tta ata Ala Thr Leu Ile 75	ggg aca gtg gcc Gly Thr Val Ala	ttc 240 Phe 80
ata gcc aga cct Ile Ala Arg Pro				Lys ·
tat ggt cgt aag Tyr Gly Arg Lys 100				
gga aca ggc ctt Gly Thr Gly Leu 115	Ser Gly Ile A	gct aca aac tta Ala Thr Asn Leu 120	tat atg ctc gca Tyr Met Leu Ala 125	gtt 384 Val
tgc cgt ttt att Cys Arg Phe Ile				

	130				135					140				
	act Thr													480
	gct Ala													528
	ata Ile													576
	ata Ile													624
-	cca Pro 210	-	_	_	 		-	-			_	-		672
	ttt Phe	_		_	_								_	720
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	cta Leu													816
	tca Ser		_	_		_					_			864
	ttt Phe 290													912
	gtc Val													960
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_	tac Tyr					_								1104
	tta Leu													1152

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		_	_		gct Ala	-		_		_				-		96
					gat Asp											144
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		Asp	Cys	Val	atc Ile 70	Val	Āla	Thr	Pro	Asn		Leu	His		Glu	240
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					acc Thr											384
					gca Ala											432

-				-			_	aga Arg				-				480
	_					-	_	aaa Lys	_							528
							_	tgt Cys 185	_	_					_	576
								ggt Gly								624
					_	-	_	atg Met			_		-	-		672
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-	-			-				gga Gly								768
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								gcc Ala	_			_	_	-	-	960
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					Lys						ctc Leu		Thr			528
	-	-	-	_			-	_			caa Gln					576

					caa Gln											624
					cgt Arg											672
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tct Ser	gta Val	cgt Arg	gct Ala 260	ggc Gly	cat His	gta Val	gat Asp	caa Gln 265	aac Asn	gat Asp	att Ile	cgg Arg	ttt Phe 270	cta Leu	gaa Glu	816
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					caa Gln 310											960
					acc Thr											1008
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					gcc Ala 390											1200
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tac ctg ccg gaa ggt tac cgc tgg gat gac ctg aaa tcc cgc atc ggc Tyr Leu Pro Glu Gly Tyr Arg Trp Asp Asp Leu Lys Ser Arg Ile Gly 50 55 60	192
cag gag cag ttg cag ttc tac cga aaa atg ctc gtg cat tta ggc gaa Gln Glu Gln Leu Gln Phe Tyr Arg Lys Met Leu Val His Leu Gly Glu 65 70 75 80	240
gat gac aaa aag ctg gta cag gca gtt ttt cat aat gtt agt acc acc Asp Asp Lys Leu Val Gln Ala Val Phe His Asn Val Ser Thr Thr 85 90 95	288
atc acc gag ccg aaa caa ata acc gca ctg gtc agc aat atg gat tcg Ile Thr Glu Pro Lys Gln Ile Thr Ala Leu Val Ser Asn Met Asp Ser 100 105 110	336
ctg gac tgg tac aac ggc gcg cac ggt aag tcg cgc gat gac ttc ggc Leu Asp Trp Tyr Asn Gly Ala His Gly Lys Ser Arg Asp Asp Phe Gly 115 120 125	384
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ggt gca ggc cag tac ttc acc ccg cgt ccg ctg att aaa acc att att	480

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acc Thr	aat Asn	gat Asp 195	ctg Leu	gac Asp	gac Asp	ctt Leu	gat Asp 200	ggc Gly	gac Asp	acg Thr	cag Gln	gat Asp 205	ttc Phe	cag Gln	atc Ile	624
	cgc Arg 210															672
	ctg Leu															720
ggc Gly	ggc Gly	gca Ala	atc Ile	cgt Arg 245	ctg Leu	ggc Gly	aac Asn	act Thr	ctg Leu 250	ggt Gly	agc Ser	gac Asp	ggt Gly	gaa Glu 255	aac Asn	768
	ccg Pro															816
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ggc Gly	acc Thr	gac Asp	att Ile	cgt Arg 325	cgt Arg	gac Asp	ctg Leu	atg Met	gat Asp 330	aag Lys	tgt Cys	cat His	ctg Leu	cac His 335	acc Thr	1008
	ctg Leu	_	_	_						-	-			_		1056
	gtg Val															1104
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Pro 385	Ser	Phe	Gly	Lys	Arg 390	Thr	Pro	Phe	Thr	Asp 395	Glu	His	Leu	Gln	Pro 400	-	
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														ctg Leu			1440
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gaa Glu	tga *																1590
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Gly	caa Gln	tca Ser	gca Ala 20	atg Met	gct Ala	agg Arg	ctt Leu	tta Leu 25	ggt Gly	gta Val	tca Ser	cct Pro	cca Pro 30	agc Ser	gta Val		96
aat Asn	caa Gln	tgg Trp	atc Ile	aaa Lys	ggg Gly	gta Val	cgt _. Arg	caa Gln	ttg Leu	cct Pro	gcc Ala	gag Glu	aga Arg	tgt Cys	cca Pro		144

35 40 45 qca att gaa cqt qca aca aga ggt gag gtt ctg tgc gaa gaa ctt cgt 192 Ala Ile Glu Arg Ala Thr Arg Gly Glu Val Leu Cys Glu Glu Leu Arg cct gat att gac tgg tca tat tta cga cgt tcg gca tgt tgt tcg cag 240 Pro Asp Ile Asp Trp Ser Tyr Leu Arg Arg Ser Ala Cys Cys Ser Gln aat atg tca gtg aag caa cta aat gac agt aac aaa tcc tca ttt gat 288 Asn Met Ser Val Lys Gln Leu Asn Asp Ser Asn Lys Ser Ser Phe Asp 297 cat acc tga His Thr <210> 262 <211> 423 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(423) <400> 262 atg aaa atc aag cat gag cac atc gaa tca gtg ttg ttt gcc cta gca 48 Met Lys Ile Lys His Glu His Ile Glu Ser Val Leu Phe Ala Leu Ala 10 gcc gaa aaa ggg cag gca tgg gta gcc aat gca att act gaa gaa tat 96 Ala Glu Lys Gly Gln Ala Trp Val Ala Asn Ala Ile Thr Glu Glu Tyr ctg cgc cag ggg ggc ggc gaa ttg ccc ctg gtt cca ggc aag gac tgg 144 Leu Arg Gln Gly Gly Glu Leu Pro Leu Val Pro Gly Lys Asp Trp 192 aac aat cag cag aat atc tat cac cgt tgg ttg aaa ggt gaa acg aaa Asn Asn Gln Gln Asn Ile Tyr His Arg Trp Leu Lys Gly Glu Thr Lys acq caa aga gaa aaa att cag aag ctg atc cca gca att ctg gca atc 240 Thr Gln Arg Glu Lys Ile Gln Lys Leu Ile Pro Ala Ile Leu Ala Ile ctt ccg cgc gag ctg cgt cac cga ctc tgc atc ttc gat acc ctg gaa 288 Leu Pro Arg Glu Leu Arg His Arg Leu Cys Ile Phe Asp Thr Leu Glu cgc cgt qca tta ctg gcg gcg cag gaa gcg tta agt acg gca att gat 336 Arg Arg Ala Leu Leu Ala Ala Gln Glu Ala Leu Ser Thr Ala Ile Asp 105 geg cat gat gat gca gtc caa gcc gtt tac egg aaa gcg cat ttc agc 384 Ala His Asp Asp Ala Val Gln Ala Val Tyr Arg Lys Ala His Phe Ser 120

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gct gac acc atg cat ttg tca gca gag gag cat ggt gcg tat ttg g Ala Asp Thr Met His Leu Ser Ala Glu Glu His Gly Ala Tyr Leu 1 35 40 45	
ctg atg ttc aat tac tgg caa aca gga aag cca ata cct aaa aac a Leu Met Phe Asn Tyr Trp Gln Thr Gly Lys Pro Ile Pro Lys Asn a 50 55 60	
ctg gca aaa att gcc cgt ctg act aac gag cga tgg gct gat gtt c Leu Ala Lys Ile Ala Arg Leu Thr Asn Glu Arg Trp Ala Asp Val 65 70 75	gaa 240 Glu 80
cca tcc ttg cag gag ttt ttt tgc gat aac ggc gag gaa tgg gtg Pro Ser Leu Gln Glu Phe Phe Cys Asp Asn Gly Glu Glu Trp Val 85 90 95	
ctt cgg att gag gaa gat ctg gca tca gtc agg gaa aaa tta acc Leu Arg Ile Glu Glu Asp Leu Ala Ser Val Arg Glu Lys Leu Thr 100 105 110	
aaa tca gcc gca gga aaa gca tct gtt cag gcc aga aga agc aga Lys Ser Ala Ala Gly Lys Ala Ser Val Gln Ala Arg Arg Ser Arg 115 120 125	
gaa gca gat gtt caa aca aaa caa gag aga aat tta aca ggt gtt glu Ala Asp Val Gln Thr Lys Gln Glu Arg Asn Leu Thr Gly Val	
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aat aaa gat aca gat aaa gat cta aaa aca gat ccc ccc cta aat Asn Lys Asp Thr Asp Lys Asp Leu Lys Thr Asp Pro Pro Leu Asn 165 170 175	

Pro Arg Gly	aat cg Asn Ar 180		-		-		-		-	_			576
ttg ccg aac Leu Pro Asn 195													624
cgc cag gca Arg Gln Ala 210													672
gcg ata cgg Ala Ile Arg 225													720
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Glu	Gly	Gln	Arg	Tyr 85	Ala	Leu	Ser	Gln	Ala 90	Lys	Ser	Ile	Ala	Asp 95	Glu	
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ggt Gly	cag Gln 130	aca Thr	gtg Val	att Ile	gtg Val	gtt Val 135	acc Thr	gtg Val	gct Ala	gat Asp	gtt Val 140	atg Met	agt Ser	gcc Ala	ctg Leu	432
cac His 145	gcc Ala	agc Ser	tat Tyr	gac Asp	gat Asp 150	ggg Gly	cag Gln	tca Ser	ggc Gly	gaa Glu 155	aaa Lys	ttt Phe	ttg Leu	cgg Arg	gaa Glu 160	480
					ctg Leu										Arg	528
gag Glu	acg Thr	aaa Lys	aac Asn 180	gag Glu	cag Gln	gtg Val	gta Val	ctg Leu 185	cac His	cag Gln	att Ile	gtt Val	gat Asp 190	cgc Arg	cgg Arg	576
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	L> Ci		. (61:	2)	٠						-	•				
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					ttt Phe											96

			20					25				30			
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							aag Lys								192
							aac Asn								240
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	-		_	-	-		agc Ser		 _	-		-	_		432
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	gct gat Ala Asp 20	gcg aaa Ala Lys										96
gtt gcc gct Val Ala Ala 35			_				-	_	_	_		144
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ccg att gaa Pro Ile Glu				Gln							336
gat tat ctc Asp Tyr Leu 115											384
ggg acg ttg Gly Thr Leu 130	-			-	_		_		-	_	432
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ggt aac ggc Gly Asn Gly											528
ġcg ctc aat Ala Leu Asn	_		-	ı Ala	_			-			576
gcc ggt gcg Ala Gly Ala 195											624
gct tcc tca Ala Ser Ser 210	-		-			_	-			-	672
acc ttt aat Thr Phe Asn 225											720
ctg gca ctg Leu Ala Leu											768
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tca Ser	gta Val	tta Leu	aaa Lys 20	ata Ile	ata Ile	ttt Phe	tta Leu	ttt Phe 25	tat Tyr	ttg Leu	ttc Phe	ctc Leu	ata Ile 30	gct Ala	aga Arg	96
tta Leu	aaa Lys	caa Gln 35	cgt Arg	tat Tyr	tcg Ser	ata Ile	cgt Arg 40	gaa Glu	att Ile	aag Lys	agg Arg	gat Asp 45	tta Leu	tgg Trp	aac Asn	144
atc Ile	aga Arg 50	gaa Glu	aac Asn	tat Tyr	tcc Ser	agc Ser 55	aac Asn	gcg Ala	gct Ala	ata Ile	gcg Ala 60	aag Lys	atc Ile	tat Tyr	tgc Cys	192
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tat Tyr	gga Gly	tgg Trp	gtt Val	cgg Arg 85	ttc Phe	ata Ile	acg Thr	ttc Phe	cca Pro 90	att Ile	atg Met	tga *	•	· ·		279
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85 90 95 act ctc ggt ggt gat ttc act ctg tta ggc ctt tct cta ccq ggc tta 336 Thr Leu Gly Gly Asp Phe Thr Leu Leu Gly Leu Ser Leu Pro Gly Leu 100 105 att act ttc tta atc ttc tgg ctg gtc aac gtt ggt ata ggt ttt ggc 384 Ile Thr Phe Leu Ile Phe Trp Leu Val Asn Val Gly Ile Gly Phe Gly ggt ggc aaa gtt tta aat aaa ttc act gcc att ctt aac ccg tgc atc 432 Gly Gly Lys Val Leu Asn Lys Phe Thr Ala Ile Leu Asn Pro Cys Ile 135 tat atc gtt ttc ggc ggt atg gcg att tgg gcg att tca ctg gtc ggg 480 Tyr Ile Val Phe Gly Gly Met Ala Ile Trp Ala Ile Ser Leu Val Gly atc ggt cca atc ttt gac tac att ccg agc ggt att cag aaa gca gaa 528 Ile Gly Pro Ile Phe Asp Tyr Ile Pro Ser Gly Ile Gln Lys Ala Glu 170 aac ggt ggc ttc ctg ttc ctg gtg gtg att aac gcg gta gtt gcg gtc 576 Asn Gly Gly Phe Leu Phe Leu Val Val Ile Asn Ala Val Val Ala Val 185 tgg geg gea eeg geg gtg age gea tee gae ttt aeg caa aac gee cae 624 Trp Ala Ala Pro Ala Val Ser Ala Ser Asp Phe Thr Gln Asn Ala His 200 tcg ttt cgt gag cag gcg ctg ggg caa acg ctg ggt tta gtt gtg gcc 672 Ser Phe Arg Glu Gln Ala Leu Gly Gln Thr Leu Gly Leu Val Val Ala 215 tat att ctg ttt gcg gtc gcc ggg gta tgt att att gcc gga gcc agt 720 Tyr Ile Leu Phe Ala Val Ala Gly Val Cys Ile Ile Ala Gly Ala Ser att cac tac ggc gct gat acc tgg aac gtg ctg gat att gtt cag cgt 768 Ile His Tyr Gly Ala Asp Thr Trp Asn Val Leu Asp Ile Val Gln Arg 245 250 tgg gac agc ctg ttc gcc tcg ttc ttt gcg gta ctg gtt att ctg atg 816 Trp Asp Ser Leu Phe Ala Ser Phe Phe Ala Val Leu Val Ile Leu Met 260 aca act atc tcc act aac gcg acc ggt aat att att cca gcc ggt tat 864 Thr Thr Ile Ser Thr Asn Ala Thr Gly Asn Ile Ile Pro Ala Gly Tyr 275 280 cag att gcc gcc att gca ccg aca aaa ctg acc tat aaa aac ggc gta 912 Gln Ile Ala Ala Ile Ala Pro Thr Lys Leu Thr Tyr Lys Asn Gly Val 290 960 ctg att gcc agt att atc agc ttg ctg atc tgc ccg tgg aaa tta atg Leu Ile Ala Ser Ile Ile Ser Leu Leu Ile Cys Pro Trp Lys Leu Met 305 320 310 gaa aat cag gac agc att tat ctt ttc ctc gat att atc ggc gga atg 1008 Glu Asn Gln Asp Ser Ile Tyr Leu Phe Leu Asp Ile Ile Gly Gly Met

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 		_	_	ggt Gly	-	_					-	_	-			336
				gaa Glu												384
			_	gct Ala			-	_		-	-	_		_		432
	-			tta Leu 150			_	-		_	-	_		-		480
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				gcg Ala												624
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	_		-	cgg Arg			-		-	-		_	-			768
				gtt Val											٠.	816
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ggt acg att aaa Gly Thr Ile Lys 340				Ala Leu	1056
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			atc Ile													144
			ccg Pro													192
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		_	atc Ile 100		_	_		_				-		_	-	336
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			ctg Leu													432
-	_	_	atc Ile	_	-		-	-				-	-	_	_	480
_			gaa Glu	_	_		-		_	_		_			_	528
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	_		ggc Gly 260				_	_		_	_	_		_		816

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	att Ile 290															912
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	ctc Leu															1344
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	atg Met															1536

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		aaa Lys														1632
		ctg Leu														1680
		ccg Pro	_	_	_					-			_	_	-	1728
		tcc Ser														1776
	-	gtg Val 595		_	_	_	_	_			-	_				1824
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		caa Gln														2016
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		gtg Val														2112
	_	gtc Val		-	-		_	-			_				-	2160
		gat Asp														2208
		aac Asn														2256

					aac Asn											2304
					ctc Leu											2352
					gtg Val 790											2400
					tcc Ser											2448
					gtg Val	_	-			_	_		-			2496
					acc Thr											2544
					ggc Gly											2592
					att Ile 870											2640
					gag Glu											2688
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					gtg Val											2784
					aac Asn											2832
		-			ggc Gly 950	_	_	-	_		-			-		2880
-	-	-	-		cgt Arg	•		_	_			_		_	-	2928
					ctg Leu											2976

	cgt Arg		Leu					Val					Val			3024
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taa *																3123
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	tcg Ser															96
	gtc Val															144
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	tcc Ser	_	_	_			_	_	-			_	_		•	288
	gac Asp															336
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Tyr	Arg 130	Lys	Ala	Asn	Pro	Ser 135	Asp	Ala	Pro	Ile	Met 140	Ile	Leu	Thr	Leu	
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								atc Ile								528
								gta Val 185								576
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								gat Asp								720
								aac Asn								768
								tca Ser 265								816
								att Ile								864
								gtt Val								912
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cag Gln	gat Asp	ege Arg	tcc Ser	ccc Pro 325	acc Thr	att Ile	cgc Arg	gcc Ala	tcg Ser 330	ctg Leu	gaa Glu	gaa Glu	gtc Val	gag Glu 335	caa Gln	1008
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								att Ile								1104
tcg	ctg	att	ggt	acg	ttt	gcg	gcg	atg	tac	ctg	tgc	gga	ttc	agt	ctc	1152

Ser	Leu 370	Ile	Gly	Thr	Phe	Ala 375	Ala	Met	Tyr	Leu	Cys 380	Gly	Phe	Ser	Leu	
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	atg Met															1296
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	acg Thr															1440
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	ggc Gly			_										_	_	1584
	ggc Gly 530															1632
	tcg Ser															1680
	ggc Gly															1728
	aag Lys															1776
-	aat Asn	_							_	_			_		_	1824
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Met	Phe 610	Ile	Thr	Leu	Lys	Pro 615	Arg	Asp	Glu	Arg	Ser 620	Glu	Thr	Ala	Gln		
			-	-	ctg Leu 630	_	-		-			-	_			192	0
					gcg Ala											196	8
_		_	-		cag Gln		_	_			-	-	_		-	201	6
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					ccg Pro											225	6
gat Asp	ccg Pro	cgc Arg 755	tat Tyr	acc Thr	cag Gln	gac Asp	atc Ile 760	agt Ser	gcg Ala	ctg Leu	gaa Glu	aaa Lys 765	atg Met	ttc Phe	gtt Val	230	4
atc Ile	aat Asn 770	aac Asn	gaa Glu	ggc Gly	aaa Lys	gcg Ala 775	atc Ile	ccg Pro	ctg Leu	tcg Ser	tat Tyr 780	ttc Phe	gct Ala	aaa Lys	tgg Trp	235	2
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gcc Ala	agt Ser	gcg Ala	gcg Ala 820	atc Ile	gat Asp	cgc Arg	gca Ala	atg Met 825	acc Thr	cag Gln	ctt Leu	ggt Gly	gtg Val 830	cct Pro	tcg Ser	249	6
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Met	Asn 850	Ser	Gln	Val	Ile	Leu 855	Ile	Ile	Ala	Ala	Ile 860	Ala	Thr	Val	Tyr	
	gtg Val															2640
	tcc Ser		-		_			_			_	_		_		2688
	ttc Phe															2736
	atc Ile				_			-		_	_	-	-			2784
	gaa Glu 930															2832
	gcc Ala															2880
	ctg Leu															2928
	ctg Leu															2976
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	cgt Arg 1010	Leu					Ser					Gln				3072
gag Glu 102	*															3078
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			atg Met			-			-	_	_	_		_			144
			gtc Val														192
			ctg Leu														240
			ctg Leu														288
			gaa Glu 100												ggc Gly	•	336
			gtg Val														384
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			ctg Leu														480
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ggt Gly	gcg Ala	atc Ile	gcc Ala 180	aca Thr	ttg Leu	ctg Leu	tta Leu	atg Met 185	ccg Pro	aac Asn	tac Tyr	acc Thr	atg Met 190	cag Gln	acg Thr		576
cgg Arg	cgc Arg	ttt Phe 195	gat Asp	ctc Leu	tcc Ser	gga Gly	ttt Phe 200	tta Leu	ttg Leu	ctg Leu	gcg Ala	gtt Val 205	ggc Gly	atg Met	gcg Ala		624
gta Val	tta Leu 210	acc Thr	ctg Leu	gcg Ala	ctg Leu	gac Asp 215	ggc Gly	agt Ser	aaa Lys	ggt Gly	aca Thr 220	ggt Gly	tta Leu	tcg Ser	ccg Pro		672
ctg Leu 225	acg Thr	att Ile	gca Ala	ggc Gly	ctg Leu 230	gtc Val	gca Ala	gtt Val	ggc Gly	gtg Val 235	gtg Val	gca Ala	ctg Leu	gtg Val	ctt Leu 240		720
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					agc Ser 310											960
		_			tat Tyr	_		-	_	-			_	_		1008
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		_	_	_	ttc Phe	_	•					_	_		_	1104
_	_				atg Met			_	_	-		_		-	-	1152
	_		-	_	ggc Gly 390		_	_	-	-	_		_		_	1200
_	_	-			gtc Val			_		_	_	_				1248
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tqq ctq qqa atc cag cag tgg cgc gcc gct ggt gca att gac ctt aaa
                                                                       96
Trp Leu Gly Ile Gln Gln Trp Arg Ala Ala Gly Ala Ile Asp Leu Lys
teg etg gee tet act caa teg egt ega eat ttg tte eag ege gea gtt
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Ser Leu Ala Ser Thr Gln Ser Arg Arg His Leu Phe Gln Arg Ala Val
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                             40
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Phe Val Asn Leu Thr Asn Pro Lys Ser Ile Val Phe Leu Ala Ala Leu
     50
                                                                      240
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Phe Pro Gln Phe Ile Met Pro Gln Gln Pro Gln Leu Met Gln Tyr Ile
                                         75
65
                     70
gtg ctc ggc gtc acc act att gtg gtc gat att att gtg atg atc ggt
                                                                      288
Val Leu Gly Val Thr Thr Ile Val Val Asp Ile Ile Val Met Ile Gly
tac gcc acc ctt gct caa cqq att gct cta tgg att aaa gga cca aag
                                                                      336
Tyr Ala Thr Leu Ala Gln Arg Ile Ala Leu Trp Ile Lys Gly Pro Lys
cag atg aag gcg ctg aat aag att ttc ggc tcg ttg ttt atg ctg gtg
                                                                      384
Gln Met Lys Ala Leu Asn Lys Ile Phe Gly Ser Leu Phe Met Leu Val
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Gly Ala Leu Leu Ala Ser Ala Arg His Ala *
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_	gtt Val	-			_	_	_	_	_				_			96
_	gcc Ala	-		_			_	_	_	_		-	_	-		144
	aaa Lys 50					_		-				_	_			192
	ctc Leu	_	_	_		_						_	_			240
	gcc Ala	_	_			_	-			_	_					288
_	aca Thr	-	-	_	_		-				_	_	_	-	_	336
_	ccg Pro		-	-		_		-				-	_			384
	tgg Trp 130			_	_				_	_		-		-	_	432
-	cat His	-		-				_		_	-	_			_	480
	gca Ala															528
	Gly ggg															576
_	tac Tyr			_	-	-	-	_			_			-	-	624
	ttc Phe 210															672
	gaa Glu															720
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gcc tgg tta ctg gtg cgt tgc acg ttt ccg ggc aaa gct ctg Ala Trp Leu Leu Val Arg Cys Thr Phe Pro Gly Lys Ala Leu 35 . 40 . 45		144											
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tat gac tgg ttt ggt att acc ttc gcc ttt agc tgg cgc ggc Tyr Asp Trp Phe Gly Ile Thr Phe Ala Phe Ser Trp Arg Gly 85 90		288											
ctc gct gcc gcc gtc atg tcg ttt ccg ctg atg gtg cgg gca Leu Ala Ala Val Met Ser Phe Pro Leu Met Val Arg Ala 100 105 110	Ile Arg	336											
ctg gcg ctg gaa ggg gtt gat gtc aaa ctg gaa cag gcc gca Leu Ala Leu Glu Gly Val Asp Val Lys Leu Glu Gln Ala Ala 115 120 125	aga aca Arg Thr	384											
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		ccg gaa aag cgt cgc Pro Glu Lys Arg Arg 75	
	a Arg Leu Phe E	ecg cat tac aaa gtg Pro His Tyr Lys Val 90	
	t Ser Lys Ser M	atg gtc gat cag ttc Met Val Asp Gln Phe 105	
		ttg ctt gac cgt tta Leu Leu Asp Arg Leu 125	
		gtg gcg att ggt cgg Val Ala Ile Gly Arg	

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	ccg Pro															528
	atc Ile															576
	cat His															624
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tgg Trp 225	ctg Leu	ccg Pro	aaa Lys	gag Glu	caa Gln 230	caa Gln	agt Ser	agc Ser	att Ile	ctg Leu 235	aaa Lys	gtg Val	acg Thr	gtg Val	ctt Leu 240	720
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caa Gln	acc Thr 290	agc Ser	att Ile	cgt Arg	aac Asn	gta Val 295	ttg Leu	cgg Arg	gca Ala	aaa Lys	gtt Val 300	gtt Val	aat Asn	agt Ser	tat Tyr	912
gac Asp 305	gac Asp	aac Asn	ggc Gly	cag Gln	gtg Val 310	gaa Glu	gtg Val	gaa Glu	ctg Leu	gaa Glu 315	gtc Val	ggc Gly	ggt Gly	aaa Lys	acg Thr 320	960
ctg Leu	tgg Trp	gcg Ala	cgt Arg	atc Ile 325	agc Ser	ccg Pro	tgg Trp	gcc Ala	agg Arg 330	gat Asp	gaa Glu	ctg Leu	gcg Ala	atc Ile 335	aaa Lys	1008
cct Pro	ggc Gly	ctg Leu	tgg Trp 340	ctg Leu	tac Tyr	gcg Ala	caa Gln	att Ile 345	aaa Lys	agt Ser	gtg Val	tcg Ser	ata Ile 350	acc Thr	gcc Ala	1056
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gcg gat act aaa aca gga ggt ttt atg aac aga acg att ctt gtc cct
                                                                       96
Ala Asp Thr Lys Thr Gly Gly Phe Met Asn Arg Thr Ile Leu Val Pro
atc gat att tcc gat tca gaa tta act caa cgc gtg att agc cac gtt
                                                                      144
Ile Asp Ile Ser Asp Ser Glu Leu Thr Gln Arg Val Ile Ser His Val
         35
                             40
gag gaa gag gca aag att gat gca gag gtt cat ttc ctg acg gta
                                                                      192
Glu Glu Glu Ala Lys Ile Asp Asp Ala Glu Val His Phe Leu Thr Val
     50
ata cct tca ctg ccc tac tat gcc tct ctg ggt tta gcg tat tcc gca
                                                                      240
Ile Pro Ser Leu Pro Tyr Tyr Ala Ser Leu Gly Leu Ala Tyr Ser Ala
gaa tta ccg gca atg gat gac ctg aaa gcg gaa gcc aaa tcg caa ctg
                                                                      288
Glu Leu Pro Ala Met Asp Asp Leu Lys Ala Glu Ala Lys Ser Gln Leu
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gaa gag atc att aaa aaa ttt aaa ctg cca acc gac aga gtg cat gtc
                                                                      336
Glu Glu Ile Ile Lys Lys Phe Lys Leu Pro Thr Asp Arg Val His Val
            100
                                105
cat gtt gag gaa ggc tcg ccc aaa gac cgc att ctg gaa ttg gcg aag
                                                                      384
His Val Glu Glu Gly Ser Pro Lys Asp Arg Ile Leu Glu Leu Ala Lys
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                                                                      432
Lys Ile Pro Ala His Met Ile Ile Ile Ala Ser His Arg Pro Asp Ile
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acc act tat ctg ctc ggt tcc aac gcc gca gct gta gtg cgt cac gca
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Thr Thr Tyr Leu Leu Gly Ser Asn Ala Ala Ala Val Val Arg His Ala
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aat gac caq Asn Asp Glr 225							_	•	- •	720
tgg act gct Trp Thr Ala		Lys Tyr					Leu A			768
atg tat toa Met Tyr Sei	-	-	Met Th	_	_		-	-		816
gct gtg gca Ala Val Ala 275	Asn Lys	_		_	-	_	-		_	864
ttt gat ttt Phe Asp Phe 290			Ala Va		Phe L					912
cgt gac cto Arg Asp Let 305										960
gat aaa gat Asp Lys Asp		Lys Tyr					Tyr :			1008
aat aaa aad Asn Lys Asr			Val As							1056
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acc Thr	ctg Leu 50	tcg Ser	caa Gln	aag Lys	ttt Phe	ggt Gly 55	att Ile	gcg Ala	gca Ala	aac Asn	att Ile 60	gat Asp	ttt Phe	ccg Pro	ctg Leu	192
cca Pro 65	gcg Ala	agc Ser	ttt Phe	atc Ile	tgg Trp 70	gat Asp	atg Met	ttc Phe	gtc Val	cgg Arg 75	gtg Val	tta Leu	ccg Pro	gaa Glu	atc Ile 80	240
ccc Pro	aaa Lys	gag Glu	agc Ser	gcc Ala 85	ttt Phe	aac Asn	aaa Lys	cag Gln	agc Ser 90	atg Met	agc Ser	tgg Trp	aaa Lys	ctg Leu 95	atg Met	288
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cat His	tat Tyr	ctg Leu 115	act Thr	gac Asp	gat Asp	agc Ser	gac Asp 120	aag Lys	cga Arg	aaa Lys	ctg Leu	ttc Phe 125	cag Gln	ctt Leu	tcc Ser	384
tca Ser	aaa Lys 130	gcg Ala	gcg Ala	gac Asp	ctg Leu	ttt Phe 135	gac Asp	cag Gln	tat Tyr	ctg Leu	gtc Val 140	tat Tyr	cgt Arg	ccg Pro	gac Asp	432
tgg Trp 145	ctg Leu	gca Ala	cag Gln	tgg Trp	gaa Glu 150	aca Thr	gga Gly	cat His	ttg Leu	gtt Val 155	gaa Glu	Gly	ctg Leu	gga Gly	gaa Glu 160	480
gca Ala	cag Gln	gcc Ala	tgg Trp	caa Gln 165	gcc Ala	ccg Pro	ttg Leu	tgg Trp	aag Lys 170	gcg Ala	ctg Leu	gtg Val	gaa Glu	tat Tyr 175	acc Thr	528
cat His	caa Gln	ctc Leu	180 Gly ggg	caa Gln	ccg Pro	cgc Arg	tgg Trp	cac His 185	cgc Arg	gcc Ala	aat Asn	ctc Leu	tat Tyr 190	cag Gln	cgc Arg	576
ttt Phe	atc Ile	gaa Glu 195	acg Thr	ctg Leu	gag Glu	tcc Ser	gcg Ala 200	acg Thr	acc Thr	tgc Cys	ccg Pro	ccg Pro 205	ggg Gly	tta Leu	cct Pro	624
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cag Gln 225	Ala	cta Leu	cag Gln	gcg Ala	ctg Leu 230	ggt Gly	aaa Lys	cat His	att Ile	gaa Glu 235	atc Ile	cat His	ctc Leu	ctg Leu	ttt Phe 240	720
acc Thr	aac Asn	ccc Pro	tgc Cys	cgt Arg 245	Tyr	tac Tyr	tgg Trp	ggc Gly	gat Asp 250	att Ile	aaa Lys	gat Asp	cct Pro	gct Ala 255	Tyr	768
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	ctt Leu															960
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	att Ile	_		-		_	-	_	_		-	_	-	_		1056
	aac Asn															1104
	ctg Leu 370	_	_	_					-	-		_	-	_	-	1152
	gtt Val															1200
	aca Thr															1248
_	tac Tyr	_	-			_	-	-			_			-	_	1296
_	tac Tyr				-			_	_	_			_			1344
	gta Val 450															1392
	gtg Val															1440
	cgg Arg															1488
	aac Asn															1536
gag	ctg	gaa	ctc	ccc	gcc	acc	gga	caa	cac	acc	tgg	cga	ttt	ggc	ctg	1584

Glu	Leu	Glu 515	Leu	Pro	Ala	Thr	Gly 520	Gln	His	Thr	Trp	Arg 525	Phe	Gly	Leu	
_	cgt Arg 530	-	-	_				-		-		-				1632
	tcg Ser	_				-	-	_	_				_	_	_	1680
	ggg Gly															1728
	ctg Leu															1776
	atg Met															1824
_	acg Thr 610	_		-				_				-	_			1872
	gcg Ala															1920
	gca Ala															1968
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	gtg Val															2064
	gcg Ala 690															2112 .
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att Ile	tcc Ser	gcg Ala	cag Gln	caa Gln 725	aaa Lys	ctc Leu	tat Tyr	atc Ile	agc Ser 730	tat Tyr	atc Ile	ggt Gly	cgt Arg	tcc Ser 735	att Ile	2208
	gat Asp															2256
gac	tac	atc	ggg	caa	agt	cat	tat	cta	ccg	ggc	gat	gaa	gcg	ctc	aac	2304

Asp	Tyr	Ile 755	Gly	Gln	Ser	His	Tyr 760	Leu	Pro	Gly	Asp	Glu 765	Ala	Leu	Asn	
														ctc Leu		2352
														cga Arg		2400
-		-	-	-					-	_	_	-		aaa Lys 815	_	2448
		_			_	_	_	-				_	_	acc Thr		2496
														gca Ala		2544
														gaa Glu		2592
	_						-	-			_	-		caa Gln		2640
	_	_		_		-	_	-	-	_	_	-	-	gaa Glu 895	-	2688
_		-	-		_		-		_		-			gct Ala		2736
														ctt Leu		2784
														att Ile		2832
														gtg Val		2880
														gcc Ala 975		2928
														ggt Gly		2976
aat	ggt	gaa	agt	cgc	ctt	ttt	cta	cgc	aaa	gac	ggc	gag	tgg	cgt	ttt	3024

Asn Gly Glu Ser Arg Leu Phe Leu Arg Lys Asp Gly Glu Trp Arg Phe 995 1000 1005	
ccg ccg ctt gca gcc gaa cag gct ttg cat tac ctc tca caa ctg att Pro Pro Leu Ala Ala Glu Gln Ala Leu His Tyr Leu Ser Gln Leu Ile 1010 1015 1020	3072
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agt ggc gcg tgg cta aaa acc tgt tat gac gcg caa aac gat gcc Ser Gly Gly Ala Trp Leu Lys Thr Cys Tyr Asp Ala Gln Asn Asp Ala 1045 1050 1055	3168
atg ctg gat gac gat tcc acg ttg caa aaa gcc cgt acg aaa ttc ctt Met Leu Asp Asp Asp Ser Thr Leu Gln Lys Ala Arg Thr Lys Phe Leu 1060 1065 1070	3216
cag gct tac gaa ggc aac atg atg gtg cgt ggc gaa ggt gat gat atc Gln Ala Tyr Glu Gly Asn Met Met Val Arg Gly Glu Gly Asp Asp Ile 1075 1080 1085	3264
tgg tat caa agg ctc tgg cgg caa tta aca cca gag aca atg gag gcc Trp Tyr Gln Arg Leu Trp Arg Gln Leu Thr Pro Glu Thr Met Glu Ala 1090 1095 1100	3312
atc gtt gaa cag tcg caa cgt ttc ctg tta ccg ctg ttt cgc ttt aat Ile Val Glu Gln Ser Gln Arg Phe Leu Leu Pro Leu Phe Arg Phe Asn 1105 1110 1115 1120	3360
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gag atg acc confidence of the Glu Met Thr A			Arg Gln *		324
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tgg cag acg co Trp Gln Thr G	-				-
gcc cag gtt to Ala Gln Val C 65		Leu Leu Ala			
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gcg tta cag cgt gaa agt tta acg agc acc cgt aag ctg gcg ctg gaa Ala Leu Gln Arg Glu Ser Leu Thr Ser Thr Arg Lys Leu Ala Leu Glu 35 40 45	144												
gat gaa atc tgg ctg cgg gta ttt acc gtc gcg aag cat ctc cag agg Asp Glu Ile Trp Leu Arg Val Phe Thr Val Ala Lys His Leu Gln Arg 50 55 60	192												
gcg ggt tat tgt cat ggc atc tgt acc ggc gaa ggg ctg gaa att gtc Ala Gly Tyr Cys His Gly Ile Cys Thr Gly Glu Gly Leu Glu Ile Val 65 70 75 80	240												
gga cag ggt gac tgt gtc att gtg cag tgg gat gcg aac agt aac ggt Gly Gln Gly Asp Cys Val Ile Val Gln Trp Asp Ala Asn Ser Asn Gly 85 90 95	288												
atc tgg gat cgc gaa ccg gta aaa gag tcc gac cag att gga ttt cgt Ile Trp Asp Arg Glu Pro Val Lys Glu Ser Asp Gln Ile Gly Phe Arg 100 105 110	336												
ctg aag gag cat gtg ctg gaa acg cta cgc ggt gcg aca tcc tgt gaa Leu Lys Glu His Val Leu Glu Thr Leu Arg Gly Ala Thr Ser Cys Glu 115 120 125	384												
ggt aag ggc tgg gat aaa gtc act aat ccg gat gcc atc att atc gac Gly Lys Gly Trp Asp Lys Val Thr Asn Pro Asp Ala Ile Ile Ile Asp 130 135 140	432												
act ttt cag gtc gta cgt cag gat gtc agc ggc ttc tcg ccg gtg ttg Thr Phe Gln Val Val Arg Gln Asp Val Ser Gly Phe Ser Pro Val Leu 145 150 155 160	480												
acg gtt aat atg cgt gct gcc agt aag tct gaa ccg caa acc gtg gtg Thr Val Asn Met Arg Ala Ala Ser Lys Ser Glu Pro Gin Thr Val Val 165 170 175	528												
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tgg cag cag tcg caa cgg cta tgg caa acc gcc agc cag gcg cgg gac Trp Gln Gln Ser Gln Arg Leu Trp Gln Thr Ala Ser Gln Ala Arg Asp 35 40 45	144											
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agt atc agc gtt atc agg gag ggg acg tta tgg tgc ctt gtg agt tcc Ser Ile Ser Val Ile Arg Glu Gly Thr Leu Trp Cys Leu Val Ser Ser 65 70 75 80	240											
gct gct ggg gcc aat acc tgt cat ggc agt tca cca ttg gtc ttt gtg Ala Ala Gly Ala Asn Thr Cys His Gly Ser Ser Pro Leu Val Phe Val 85 90 95	288											
cca cgc tgg ccc gaa gtc gaa atg agc gac ctg aca cct tcg ctt gct Pro Arg Trp Pro Glu Val Glu Met Ser Asp Leu Thr Pro Ser Leu Ala 100 105 110	336											
ttc ttt ggc ctg cgc aat acc gca tgg gcc ggg cat att cgc ttc aaa Phe Phe Gly Leu Arg Asn Thr Ala Trp Ala Gly His Ile Arg Phe Lys 115 120 125	384											
aac tca acg ggc gag tgg tgg ctg gtg gtt tcg ccg tgg gga aga ctc Asn Ser Thr Gly Glu Trp Trp Leu Val Val Ser Pro Trp Gly Arg Leu 130 135 140	432											
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	-		tgg Trp 20	_			-		-		-	_	-		96
			gcc Ala												144
			gcc Ala												192
			ggc Gly												240
-		_	gaa Glu	_		_	_	_	_			-		-	288
-			atc Ile 100		_	_	_				_				336
_	-	_	gaa Glu	_	_					_	-				384
			acc Thr												432
			aac Asn		_	_	_			_	_	_		_	480
			ttg Leu												528
			gag Glu 180												576
			gcg Ala												624
			tcc Ser												672
			ccg Pro												720
			ggg Gly												768

	245	250	2	255
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aac gat cag gaa Asn Asp Gln Glu 275	_	n Ile Ser Leu		
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caa acc gat atc Gln Thr Asp Ile 305			Val Val Arg G	
cga tat ctt tcg Arg Tyr Leu Ser			Phe Pro Leu G	
tgg ctg cgc agt Trp Leu Arg Ser 340	-			•
atg ctg tta ttc Met Leu Leu Phe 355		u Asp Met Pro		
tca tgg atg aaa Ser Trp Met Lys 370				
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acg gga atg tgt Thr Gly Met Cys			Trp Ser Ala I	
aat tca cct ttt Asn Ser Pro Phe 420				_
gcc cgc tca ttg Ala Arg Ser Leu 435		u Ser Glu Leu		
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atg gta ttg ctt Met Val Leu Leu		-		

			485					490					495			
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aat cte Asn Le																1584
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gaa to Glu Se 545																1680
cat gad His Gl	a acg ı Thr	gcg Ala	cga Arg 565	gcg Ala	gca Ala	caa Gln	tca Ser	cta Leu 570	aac Asn	agt Ser	ccg Pro	gcc Ala	ccc Pro 575	ggc Gly		1728
gga tt															÷ .	1776
tgg cc Trp Pr	t tcg Ser 595	gca Ala	tca Ser	ctt Leu	tac Tyr	gac Asp 600	tac Tyr	ccg Pro	ccg Pro	caa Gln	gaa Glu 605	cag Gln	tgg Trp	aac Asn		1824
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gag at Glu Il 69	e Gln	gcc Ala	tat Tyr	tat Tyr	gaa Glu 695	agc Ser	tgc Cys	ctg Leu	aạc Asn	ccg Pro 700	caa Gln	ctg Leu	atc Ile	acc Thr		2112
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acg gtg att gta aag go Thr Val Ile Val Lys Al 65		g Arg Pro Ala Ser	
gca gcc ttg ctg tat ga Ala Ala Leu Leu Tyr Gl 85			
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-269- . .

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_	_	ctg Leu	_			-	_			-	_	-	_		-	192
		atc Ile														240
_		aac Asn					_	_	_	_				_		288
_		gaa Glu			-		-	_	_		_	-	_			336
		gtg Val 115						_	_	-		-	_		-	384
	-	gtt Val		_	_		-		_		_	_	_	_	_	432
		atg Met														480
ggc Gly	gac Asp	gta Val	gac Asp	ggc Gly 165	aaa Lys	ccg Pro	gct Ala	gca Ala	ggc Gly 170	ggt Gly	atg Met	ttg Leu	ttg Leu	cag Gln 175	gta Val	528
		gcg Ala														576
		gaa Glu 195														624
gaa	gtg	ttg	tgg	cgt	ttg	tat	cac	gaa	gaa	gag	gtg	acg	gtt	tac	gat	672

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Glu Val Leu Trp 210	-	Tyr His 215	Glu Glu	Glu Val 220	Thr V	al Tyr	Asp	
ccg cag gat gtg Pro Gln Asp Val 225								720
gat gcg ctg aaa Asp Ala Leu Lys	acg ctg Thr Leu 245	cct gat Pro Asp	gaa gaa Glu Glu 250	gtt gat Val Asp	agc a Ser I	tc ctg le Leu 255	gcg Ala	768
gaa gat ggc gaa Glu Asp Gly Glu 260	_	-		_	Gly A			816
ctg ttc aat gcg Leu Phe Asn Ala 275								864
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			atc Ile													144
			aat Asn	-	_	_	-		_			_	-	_	-	192
			cgc Arg							_	_		-			240
			acc Thr													288
			gag Glu 100													336
			gtt Val													384
_	-	_	aaa Lys	_	-	-				_						432
-			aaa Lys		_			-		-			-	_	_	480
-	_	-	gtc Val	_					-		_	-				528

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		ctt gag ggt Leu Glu Gly 215	Ile Thr			672
_		tac ata ggg Tyr Ile Gly				720
		atg att tta Met Ile Leu	-			768
		tca cta ctt Ser Leu Leu 265	Val Ser		e Leu Gly	816
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	Ile Lys Pro	tta att gaa Leu Ile Glu 40				144

						aaa Lys 55										192
						tca Ser										240
						act Thr										288
				-		tat Tyr										336
					_	agg Arg		-								384
	-			_		tct Ser 135				-		_		-		432
						gtt Val							_			480
			-			aat Asn			-		_				•	528
_						gct Ala										576
						att Ile			-	_						624
		_		_		gtg Val 215	-	_						_		672
					-	gtt Val	-			_			_			720
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	_	-	-	_	_	gtt Val			-	-						816
_					-	acc Thr			_	_		_	_	_		864

gaa Glu	tct Ser 290	cat His	aaa Lys	gat Asp	gaa Glu	acg Thr 295	ttt Phe	tcg Ser	aat Asn	gca Ala	ctc Leu 300	ttt Phe	tta Leu	ttg Leu	gtt Val	912
					atc Ile 310											960
					aat Asn											1008
					aac Asn											1056
					att Ile											1104
					aga Arg											1152
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aaa	tgg	gtg	acg	gat	acc	gag	gca	cag	cat	agc	gtc	gca	gta	gat	gca	144

гàг	Trp	Val 35	Thr	Asp	Thr	Glu	Ala 40	Gln	His	Ser	Val	Ala 45	Val	Asp	Ala	
				cgc Arg												192
agt Ser 65	ctg Leu	att Ile	caa Gln	ctg Leu	aaa Lys 70	tta Leu	cag Gln	gct Ala	ggg	cgg Arg 75	aag Lys	ctg Leu	atg Met	cag Gln	gca Ala 80	240
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100		105	110
		cta tcc ccc cgc gtc Leu Ser Pro Arg Val 125	Thr Arg His
		tct acc ctt ctc aaa Ser Thr Leu Leu Lys 140	
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		gcg gaa atg gac gaa Ala Glu Met Asp Glu 45	Gln Trp Gly
tac gtc ggg gct aa Tyr Val Gly Ala Ly 50	a tcg cgc cag s Ser Arg Gln 55	cgc tgg ctg ttt tac Arg Trp Leu Phe Tyr 60	gcg tat gac 192 Ala Tyr Asp
agg ctc cgg aag ac Arg Leu Arg Lys Th 65	g gtt gtt gcg r Val Val Ala 70	cac gta ttc ggt gaa His Val Phe Gly Glu 75	cgc act atg 240 Arg Thr Met 80
Ala Thr Leu Gly Ar	t ctt atg agc g Leu Met Ser 5	ctg ctg tca ccc ttt Leu Leu Ser Pro Phe 90	gac gtg gtg 288 Asp Val Val 95
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aag ctg cac gta at Lys Leu His Val Il 115	c agc aag cga e Ser Lys Arg . 120	tat acg cag cga att Tyr Thr Gln Arg Ile 125	Glu Arg His
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	gtg Val															96
	cac His															144
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	tgc Cys															240
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ggt	agc	att	gtt	cag	ggt	tca	gcc	ggg	gtg	cgc	att	ggt	gcc	ccc	acc	96

Gly	Ser	Ile	Val 20	Gln	Gly	Ser	Ala	Gly 25	Val	Arg	Ile	Gly	Ala 30	Pro	Thr	
ggc Gly	gtg Val	gcc Ala 35	tgt Cys	tcg Ser	gtg Val	tgc Cys	ccc Pro 40	ggc Gly	gga Gly	gtg Val	acg Thr	tcc Ser 45	ggc Gly	cat His	ccg Pro	144
					ggt Gly											192
gcc Ala 65	ctg Leu	ccc Pro	ggc Gly	ccg Pro	ctg Leu 70	ccg Pro	ttc Phe	atc Ile	ctc Leu	tcc Ser 75	cgc Arg	acc Thr	tac Tyr	agc Ser	agt Ser 80	240
tac Tyr	cgg Arg	aca Thr	aaa Lys	acg Thr 85	ccc Pro	gcg Ala	ccg Pro	gtg Val	ggg Gly 90	agc Ser	ctc Leu	ggc Gly	ccc Pro	ggc Gly 95	tgg Trp	288
					atc Ile											336
					ggc Gly											384
ggt Gly	gag Glu 130	gac Asp	ggt Gly	tac Tyr	agc Ser	cgc Arg 135	agc Ser	gag Glu	tca Ser	ctg Leu	tgg Trp 140	ctg Leu	gtg Val	cgc Arg	ggc Gly	432
ggc Gly 145	gtg Val	gcg Ala	aaa Lys	ctg Leu	gat Asp 150	gaa Glu	ggt Gly	cac His	cgg Arg	ctg Leu 155	gcc Ala	gca Ala	ctc Leu	tgg Trp	cag Gln 160	480
gcg Ala	ctg Leu	ccg Pro	gaa Glu	gaa Glu 165	ctc Leu	cgc Arg	tta Leu	agt Ser	ccg Pro 170	cat His	cgt Arg	tat Tyr	ctg Leu	gcg Ala 175	aca Thr	528
aac Asn	agt Ser	ccg Pro	cag Gln 180	ggg Gly	ccg Pro	tgg Trp	tgg Trp	ctg Leu 185	ctc Leu	ggt Gly	tgg Trp	tgt Cys	gag Glu 190	cgg Arg	gtg Val	576
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Glu	Glu	Ala	Arg 260	Gln	Gln	Ala	Ile	Ser 265	Gly	Gly	Thr	Glu	Pro 270	Ser	Ala	
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						tgg Trp 295										912
						ctg Leu										960
						gac Asp										1008
						cgg Arg										1056
						tac Tyr										1104
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						cac His										1440
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Gln	Glu	Thr	Ala 500	Pro	Asp	Gly	Asp	Ile 505	Thr	Arg	Tyr	Arg	Tyr 510	Asp	Asn	
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					agc Ser											1632
_				•	acc Thr 550	_		_		-	_			_	_	1680
					gag Glu											1728
_	_		-		att Ile	_			-	_	-			-	_	1776
					atc Ile											1824
_		_	_		GJ y ggg		_		_				-	-	-	1872
					ggg Gly 630											1920
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					gac Asp											2016
					cac His											2064
gag Glu	gat Asp 690	gag Glu	ggt Gly	ctg Leu	gtc Val	acc Thr 695	cac His	tgg Trp	cac His	tat Tyr	gac 'Asp 700	gaa Glu	gca Ala	gac Asp	cgc Arg	2112
ctc Leu 705	acg Thr	cac	cgc Arg	acc Thr	gtg Val 710	aag Lys	ggt Gly	gaa Glu	acc Thr	gca Ala 715	gag Glu	cgg Arg	tgg Trp	cag Gln	tat Tyr 720	2160
					ctg Leu											2208 ·
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Arg	Val	Ala	Val 740	His	Tyr	Arg	Tyr	Asp 745	Glu	Lys	Gly	Arg	Leu 750	Thr	Gly	
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		acc Thr														2352
		gac Asp														2400
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		ctg Leu														2592
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		atc Ile														2736
		ctg Leu 915														2784
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		gag Glu														2880
		cgg Arg														2928
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	tac Tyr		Pro					Val					Trp			3024
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	tgg Trp				-	ĞÎy			_		Thr		_		-	3120
_	acc Thr	_		_	Thr			_	_	Gly	_		_		Leu	3168
	aga Arg	_	_	Thr	_				Leu			-	_	Arg	_	3216
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	ccg Pro		Ala					Glu					Trp			3504
	tac Tyr 1170	Asp					Leu					Asn				3552
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	ctg Leu				Arg		_			Asp	_	_	_		Arg	3648
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	cag Gln					Asp					Āla					3840
	aac Asn				Ser					Asp					Asn	3888
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	gca Ala		Thr					Arg					Ile			3984
-	ttc Phe 1330	Trp	-	-			Lys		-	-	-	Asp	-		_	4032
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														ttg Leu 95		288
														gca Ala		 336
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														aat Asn		432
														gca Ala		480
														gtc Val 175		528
														agt Ser		576
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														agg Arg		672
tta Leu 225	tct Ser	gtt Val	tta Leu	tgc Cys	gat Asp 230	gag Glu	tta Leu	aaa Lys	aaa Lys	aat Asn 235	act Thr	gtt Val	tat Tyr	gat Asp	gat Asp 240	720
atc Ile	att Ile	gaa Glu	gct Ala	gcg Ala 245	ggt Gly	gaa Glu	tta Leu	ggt Gly	gat Asp 250	aaa Lys	acg Thr	cta Leu	ctt Leu	cct Pro 255	gtt Val	768
tta Leu	gat Asp	act Thr	atg Met	ttg Leu	tac Tyr	aag Lys	ttt Phe	gat Asp	gac Asp	aat Asn	gaa Glu	att Ile	ata Ile	act Thr	tcc Ser	816

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			agc Ser 20													96
			aac Asn													144
	_		cac His	_	_		_		_	_	-	_			_	192
			aca Thr													240
			gaa Glu													288
-		_	cag Gln 100		-	_				_				-		336
			gac Asp													384
			ggg Gly													432
			gat Asp													480
-	_		atc Ile			-	_	-							-	528

ttc Phe	aca Thr	atc Ile	ggg Gly 180	ggg Gly	cat His	ggt Gly	acc Thr	ccc Pro 185	aca Thr	tct Ser	att Ile	gaa Glu	tcc Ser 190	gca Ala	acg Thr	5	576
					gct Ala											(624
ggg Gly	aat Asn 210	tat Tyr	aaa Lys	gat Asp	Gly	atg Met 215	aca Thr	gtt Val	tgg Trp	tta Leu	ttt Phe 220	tct Ser	tgt Cys	aat Asn	aca Thr	(672
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Leu	Pro	Pro 35	Ala	GLy	Ser	Arg	Leu 40	Val	Gly	Glu	Asn	Lys 45	Phe	His	Val		
Val	Glu 50	Asn	Asp	Gly	Gly	Ser 55	Leu	Glu	Ala	Ile	Ala 60	Lys	Lys	Tyr	Asn		
65					Leu 70					75	_				BO		
		_		85	Ser				90					95			
			100		Glu			105					110				
		115			Pro		120					125					
_	130				Gly	135					140						
Thr 145	Val	Ser	Asp	rys	Arg 150	Ата	Asn	Pro	Thr	155	Thr	Pro	Thr	Ala	Asn 160		
	Arg	Ala	Arg	Tyr 165	Lys	Ala	Gln	Gly	Ile 170		Leu	Pro	Ala	Val 175	Val		
		_	180		Asn			185					190				
Ala	Tyr	Gly 195	Gly	Val	Tyr	Leu	Leu 200	His	Gly	Thr	Asn	Ala 205	Asp	Phe	Gly		
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11e 225	Lys	Thr	Leu	Phe	Ser 230	Gln	Val	Thr	Pro	Gly 235	Thr	Lys	Val	Asn	11e 240		
	Asn	Thr	Pro	Ile 245	Lys	Val	Ser	Ala	Glu 250		Asn	Gly	Ala	Arg 255			
Val	Glu	Val	His 260		Pro	Leu	Ser	Glu 265		Ile	Asp	Asp	Asp 270		Gln		
Leu	Leu	Pro 275		Thr	Leu	Asn	Ser 280		Met	Gln	Ser	Phe 285	Ľуs	Asp	Ala		

Ala Gln Thr Asp Ala Glu Val Met Gln His Val Met Asp Val Arg Ser 295 Gly Met Pro Val Asp Val Arg Arg His Gln Val Ser Pro Gln Thr Leu 315 <210> 300 <211> 728 <212> PRT <213> Escherichia coli <400> 300 Met Ile Thr Arg Ile Pro Arg Ser Ser Phe Ser Ala Asn Ile Asn Asn Thr Ala Gln Thr Asn Glu His Gln Thr Leu Ser Glu Leu Phe Tyr Lys 20 25 Glu Leu Glu Asp Lys Phe Ser Gly Lys Glu Leu Ala Thr Pro Leu Leu 40 Lys Ser Phe Ser Glu Asn Cys Arg Gln Asn Gly Arg His Ile Phe Ser 60 Asn Lys Asp Phe Val Ile Lys Phe Ser Thr Ser Val Leu Gln Ala Asp 75 70 Lys Lys Glu Ile Thr Ile Ile Asn Lys Asn Glu Asn Thr Thr Leu Thr 90 85 Gln Thr Ile Ala Pro Ile Phe Glu Lys Tyr Leu Met Glu Ile Leu Pro 105 Gln Arq Ser Asp Thr Leu Asp Lys Gln Glu Leu Asn Leu Lys Ser Asp 120 125 Arg Lys Glu Lys Glu Phe Pro Arg Ile Lys Leu Asn Gly Gln Cys Tyr 140 135 Phe Pro Gly Arg Pro Gln Asn Arg Ile Val Cys Arg His Ile Ala Ala 155 150 Gln Tyr Ile Asn Asp Ile Tyr Gln Asn Val Asp Tyr Lys Pro His Gln 165 170 Asp Asp Tyr Ser Ser Ala Glu Lys Phe Leu Thr His Phe Asn Lys Lys 180 185 Cys Lys Asn Gln Thr Leu Ala Leu Val Ser Ser Arg Pro Glu Gly Arg 200 195 Cys Val Ala Ala Cys Gly Asp Phe Gly Leu Val Met Lys Ala Tyr Phe 215 Asp Lys Met Glu Ser Asn Gly Ile Ser Val Met Ala Ala Ile Leu Leu 230 235 Val Asp Asn His Ala Leu Thr Val Arg Leu Arg Ile Lys Asn Thr Thr 250 245 Glu Gly Cys Thr His Tyr Val Val Ser Val Tyr Asp Pro Asn Val Thr 265 Asn Asp Lys Ile Arg Ile Met Ser Glu Ser Lys Glu Asn Ile Lys His 280 Tyr Ser Leu Met Asp Phe Met Asn Val Asp Tyr Ser Leu Leu Lys Trp 300 295 Ser Asn Asp His Val Ile Asn Gln Ser Val Ala Ile Ile Pro Ala Leu 310 315 Pro Lys Glu Gln Leu Leu Met Leu Lys Gly Ser Val Asp Glu Ile Thr 325 330 Pro Pro Leu Ser Pro Ala Thr Met Asn Leu Leu Met Ala Ile Gly Gln 345 Asn His Gln Leu Thr Gln Leu Met Ile Gln Leu Gln Lys Met Pro Glu 360 365 Leu His Arg Thr Glu Met Leu Thr Ala Tyr Asn Ser Ile Asn Leu Pro 380 375 Gly Leu Tyr Leu Ala Ile Asn Tyr Gly Asn Ala Asp Ile Val Glu Thr

390

```
Ile Phe Asn Ser Leu Ser Glu Thr Gly Tyr Glu Gly Leu Leu Ser Lys
                              410
       405
Lys Asn Leu Met His Ile Leu Glu Ala Lys Asp Lys Asn Gly Phe Ser
                                     430
                           425
Gly Leu Phe Leu Ala Ile Ser Arg Lys Asp Lys Asn Val Val Thr Ser
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                                445
Ile Leu Asn Ala Leu Pro Lys Leu Ala Ala Thr His His Leu Asp Asn
 450 455
                                     460
Glu Gln Val Tyr Lys Phe Leu Ser Ala Lys Asn Arg Thr Ser Ser His
                                  475
                470
Val Leu Tyr His Val Met Ala Asn Gly Asp Ala Asp Met Leu Lys Ile
             485
                               490
                                                495
Val Leu Asn Ala Leu Pro Leu Leu Ile Arg Thr Cys His Leu Thr Lys
                            505
          500
Glu Gln Val Leu Asp Leu Leu Lys Ala Lys Asp Phe Tyr Gly Cys Pro
                        520
                                         525
Gly Leu Tyr Leu Ala Met Gln Asn Gly His Ser Asp Ile Val Lys Val
                   535
                                      540
Ile Leu Glu Ala Leu Pro Ser Leu Ala Gln Glu Ile Asn Ile Ser Ala
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                                  555
Ser Asp Ile Val Asp Leu Leu Thr Ala Lys Ser Leu Ala Arg Asp Thr
           565
                               570
Gly Leu Phe Met Ala Met Gln Arg Gly His Met Asn Val Ile Asn Thr
         580
                            585
Ile Phe Asn Ala Leu Pro Thr Leu Phe Asn Thr Phe Lys Phe Asp Lys
                        600
                                605
Lys Asn Met Lys Pro Leu Leu Leu Ala Asn Asn Ser Asn Glu Tyr Pro
                                   620
                    615
Gly Leu Phe Ser Ala Ile Gln His Lys Gln Gln Asn Val Val Glu Thr
625 630
                                635
Val Tyr Leu Ala Leu Ser Asp His Ala Arg Leu Phe Gly Phe Thr Ala
                              650
           645
Glu Asp Ile Met Asp Phe Trp Gln His Lys Ala Pro Gln Lys Tyr Ser
                 665
Ala Phe Glu Leu Ala Phe Glu Phe Gly His Arg Val Ile Ala Glu Leu
                     680
Ile Leu Asn Thr Leu Asn Lys Met Ala Glu Ser Phe Gly Phe Thr Asp
  690 695
Asn Pro Arg Tyr Ile Ala Glu Lys Asn Tyr Met Glu Ala Leu Leu Lys
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Lys Ala Ser Pro His Thr Val Arg
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<211> 84
<212> PRT
<213> Escherichia coli
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Met Glu Lys Ser Ile Val Val Ala Ile Glu Arg Phe Val Lys His Pro
         20 .
                           25
Ile Tyr Gly Lys Phe Ile Lys Arg Thr Thr Lys Leu His Val His Asp
                       40
                                         45
Glu Asn Asn Glu Cys Gly Ile Gly Asp Val Val Glu Ile Arg Glu Cys
                                      60
                     55
Arg Pro Leu Ser Lys Thr Lys Ser Trp Thr Leu Val Arg Val Val Glu
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Lys Ala Val Leu

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Gly Glu Asp Val Glu Lys Leu Arg Lys Val Val Ala Asp Ile Ala Gly

```
90
               85
Val Pro Ala Gln Ile Asn Ile Ala Glu Val Arg Lys Pro Glu Leu Asp
                             105
Ala Lys Leu Val Ala Asp Ser Ile Thr Ser Gln Leu Glu Arg Arg Val
                          120
Met Phe Arg Arg Ala Met Lys Arg Ala Val Gln Asn Ala Met Arg Leu
              135
                                        140
Gly Ala Lys Gly Ile Lys Val Glu Val Ser Gly Arg Leu Gly Gly Ala
                 150
                                     155
Glu Ile Ala Arg Thr Glu Trp Tyr Arg Glu Gly Arg Val Pro Leu His
                                  170
Thr Leu Arg Ala Asp Ile Asp Tyr Asn Thr Ser Glu Ala His Thr Thr
           180
                              185
Tyr Gly Val Ile Gly Val Lys Val Trp Ile Phe Lys Gly Glu Ile Leu
                           200 . 205
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Gly Gly Met Ala Ala Val Glu Gln Pro Glu Lys Pro Ala Ala Gln Pro
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Lys Lys Gln Gln Arg Lys Gly Arg Lys
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Met Glu Thr Ile Ala Lys His Arg His Ala Arg Ser Ser Ala Gln Lys
Val Arg Leu Val Ala Asp Leu Ile Arg Gly Lys Lys Val Ser Gln Ala
Leu Asp Ile Leu Thr Tyr Thr Asn Lys Lys Ala Ala Val Leu Val Lys
                          40
Lys Val Leu Glu Ser Ala Ile Ala Asn Ala Glu His Asn Asp Gly Ala
                      55
                                          60
Asp Ile Asp Asp Leu Lys Val Thr Lys Ile Phe Val Asp Glu Gly Pro
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Ser Met Lys Arg Ile Met Pro Arg Ala Lys Gly Arg Ala Asp Arg Ile
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Leu Lys Arg Thr Ser His Ile Thr Val Val Val Ser Asp Arg
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Met Pro Arg Ser Leu Lys Lys Gly Pro Phe Ile Asp Leu His Leu Leu
Lys Lys Val Glu Lys Ala Val Glu Ser Gly Asp Lys Lys Pro Leu Arg
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Thr Trp Ser Arg Arg Ser Thr Ile Phe Pro Asn Met Ile Gly Leu Thr
                          40
Ile Ala Val His Asn Gly Arg Gln His Val Pro Val Phe Val Thr Asp
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Glu Met Val Gly His Lys Leu Gly Glu Phe Ala Pro Thr Arg Thr Tyr
Arg Gly His Ala Ala Asp Lys Lys Ala Lys Lys
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<213> Escherichia coli
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Met Ala Val Val Lys Cys Lys Pro Thr Ser Pro Gly Arg Arg His Val
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Val Lys Val Val Asn Pro Glu Leu His Lys Gly Lys Pro Phe Ala Pro
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Leu Leu Glu Lys Asn Ser Lys Ser Gly Gly Arg Asn Asn Asn Gly Arg
Ile Thr Thr Arg His Ile Gly Gly Gly His Lys Gln Ala Tyr Arg Ile
Val Asp Phe Lys Arg Asn Lys Asp Gly Ile Pro Ala Val Val Glu Arg
                                       75
Leu Glu Tyr Asp Pro Asn Arg Ser Ala Asn Ile Ala Leu Val Leu Tyr
Lys Asp Gly Glu Arg Arg Tyr Ile Leu Ala Pro Lys Gly Leu Lys Ala
                               105
Gly Asp Gln Ile Gln Ser Gly Val Asp Ala Ala Ile Lys Pro Gly Asn
                          120
                                              125
Thr Leu Pro Met Arg Asn Ile Pro Val Gly Ser Thr Val His Asn Val
                      135
                                          140
Glu Met Lys Pro Gly Lys Gly Gly Gln Leu Ala Arg Ser Ala Gly Thr
                   150
                                      155
Tyr Val Gln Ile Val Ala Arg Asp Gly Ala Tyr Val Thr Leu Arg Leu
                                  170
               165
Arg Ser Gly Glu Met Arg Lys Val Glu Ala Asp Cys Arg Ala Thr Leu
           180
                               185
Gly Glu Val Gly Asn Ala Glu His Met Leu Arg Val Leu Gly Lys Ala
                           200
Gly Ala Ala Arg Trp Arg Gly Val Arg Pro Thr Val Arg Gly Thr Ala
                       215
                                           220
Met Asn Pro Val Asp His Pro His Gly Gly Glu Gly Arg Asn Phe
                  230
                                       235
Gly Lys His Pro Val Thr Pro Trp Gly Val Gln Thr Lys Gly Lys Lys
                                  250
Thr Arg Ser Asn Lys Arg Thr Asp Lys Phe Ile Val Arg Arg Arg Ser
                               265
Lys
<210> 308
<211> 100
<212> PRT
<213> Escherichia coli
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Met Ile Arg Glu Glu Arg Leu Leu Lys Val Leu Arg Ala Pro His Val
Ser Glu Lys Ala Ser Thr Ala Met Glu Lys Ser Asn Thr Ile Val Leu
                               25
Lys Val Ala Lys Asp Ala Thr Lys Ala Glu Ile Lys Ala Ala Val Gln
                           40
Lys Leu Phe Glu Val Glu Val Glu Val Asn Thr Leu Val Val Lys
                . 55
Gly Lys Val Lys Arg His Gly Gln Arg Ile Gly Arg Arg Ser Asp Trp
                   70
                                   75
Lys Lys Ala Tyr Val Thr Leu Lys Glu Gly Gln Asn Leu Asp Phe Val
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WO 01/34810 90 95 Gly Gly Ala Glu <210> 309 <211> 201 <212> PRT <213> Escherichia coli <400> 309 Met Glu Leu Val Leu Lys Asp Ala Gln Ser Ala Leu Thr Val Ser Glu 10 Thr Thr Phe Gly Arg Asp Phe Asn Glu Ala Leu Val His Gln Val Val 25 Val Ala Tyr Ala Ala Gly Ala Arg Gln Gly Thr Arg Ala Gln Lys Thr Arg Ala Glu Val Thr Gly Ser Gly Lys Lys Pro Trp Arg Gln Lys Gly 55 Thr Gly Arg Ala Arg Ser Gly Ser Ile Lys Ser Pro Ile Trp Arg Ser 70 75 Gly Gly Val Thr Phe Ala Ala Arg Pro Gln Asp His Ser Gln Lys Val 90 Asn Lys Lys Met Tyr Arg Gly Ala Leu Lys Ser Ile Leu Ser Glu Leu 100 105 110 . 120 125

 Val
 Arg
 Gln
 Asp
 Arg
 Leu
 Ile
 Val
 Val
 Glu
 Lys
 Phe
 Ser
 Val
 Glu
 Ala

 Pro
 Lys
 Thr
 Lys
 Leu
 Leu
 Ala
 Gln
 Lys
 Leu
 Lys
 Asp
 Met
 Ala
 Leu
 Glu

 Asp
 Val
 Leu
 Ile
 Ile
 Thr
 Gly
 Glu
 Leu
 Asp
 Glu
 Asn
 Leu
 Phe
 Leu
 Ala

 Ala
 Arg
 Asn
 Leu
 His
 Lys
 Val
 Asp
 Ala
 Thr
 Gly
 Ile
 Asp
 Asp
 Ala
 Thr
 Gly
 Ile
 Asp
 Ile
 Asp
 Asp
 Ala
 Thr
 Gly
 Ile
 Asp
 Ile
 Asp
 Asp
 Asp
 Ala
 Thr
 Gly
 Ile
 Asp
 Ile
 Ile
 Asp
 I

Val Lys Gln Val Glu Glu Met Leu Ala

<210> 310

<211> 209

<212> PRT

<213> Escherichia coli

<400> 310

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135
                                          140
Ser Ile Gly Gln Asn Gln Thr Pro Gly Lys Val Phe Lys Gly Lys Lys
                  150
                                      155
Met Ala Gly Gln Met Gly Asn Glu Arg Val Thr Val Gln Ser Leu Asp
               165
                                   170
Val Val Arg Val Asp Ala Glu Arg Asn Leu Leu Leu Val Lys Gly Ala
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                            185
Val Pro Gly Ala Thr Gly Ser Asp Leu Ile Val Lys Pro Ala Val Lys
Ala
<210> 311
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<212> PRT
<213> Escherichia coli
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Leu Ile Asp Gln Ala Thr Ala Glu Ile Val Glu Thr Ala Lys Arg Thr
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Gly Ala Gln Val Arg Gly Pro Ile Pro Leu Pro Thr Arg Lys Glu Arg
                           40
Phe Thr Val Leu Ile Ser Pro His Val Asn Lys Asp Ala Arg Asp Gln
                       55
Tyr Glu Ile Arg Thr His Leu Arg Leu Val Asp Ile Val Glu Pro Thr
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                                      75
Glu Lys Thr Val Asp Ala Leu Met Arg Leu Asp Leu Ala Ala Gly Val
Asp Val Gln Ile Ser Leu Gly
           100
<210> 312
<211> 1569
<212> PRT
<213> Escherichia coli
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Trp Cys Leu Trp Ala Asp Val Ala Ala Lys Leu Arg Ser Leu Lys Arg
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                               25
Tyr Ser Val Phe Thr Phe Gln Arg Met Lys Phe Met Asn Arg Thr Ser
                          40
Pro Tyr Tyr Cys Arg Arg Ser Val Leu Ser Leu Leu Ile Ser Ala Leu
                       55
Ile Tyr Ala Pro Pro Gly Met Ala Ala Phe Thr Thr Asn Val Ile Gly
                   70
                                      75
Val Val Asn Asp Glu Thr Val Asp Gly Asn Gln Lys Val Asp Glu Arg
                                   90
Gly Thr Thr Asn Asn Thr His Ile Ile Asn His Gly Gln Gln Asn Val
                               105
His Gly Gly Val Ser Asn Gly Ser Leu Ile Glu Ser Gly Gly Tyr Gln
                         120
Asp Ile Gly Ser His Asn Asn Phe Val Gly Gln Ala Asn Asn Thr Thr
             135
                                          140
Ile Asn Gly Gly Arg Gln Ser Ile His Asp Gly Gly Ile Ser Thr Gly
                  150 155
Thr Thr Ile Glu Ser Gly Asn Gln Asp Val Tyr Lys Gly Gly Ile Ser
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-294-

				165					170					175	
Asn	Gly	Thr	Thr 180		Lys	Gly	Gly	Ala 185	Ser	Arg	Val	Glu	Gly 190		Ser
Ala	Asn	Gly 195	Ile	Leu	Ile	Asp	Gly 200	Gly	Ser	Gln	Ile	Val 205	Lys	Val	Gln
Gly	His 210	Ala	Asp	Gly	Thr	Thr 215	Ile	Asn	Lys	Ser	Gly 220	Ser	Gln	Asp	Val
Val 225	Gln	Gly	Ser	Leu	Ala 230	Thr	Asn	Thr	Thr	Ile 235	Asn	Gly	Gly	Arg	Gln 240
				245	Thr				250					255	_
		-	260		Glu			265					270		_
		275			Asn		280					285			
	290	_			Gln	295					300				
305					Gly 310					315					320
				325	His				330		_			335	
_			340		Gly Asn			345		_			350		
		355			Ser		360					365			
	370				Thr	375					380	_	_	_	_
385					390 Asp					395			_		400
	_			405	Asn				410					415	
	_	_	420		Thr			425					430		
		435		_	Ser		440					445			
	450				Asn	455					460				
465			_		470 His					475					480
				485	Ala				490					495	
			500		Thr			505					510		
		515			Thr		520					525			
	530				Gly	535					540				
545				_	550 Asn					555					560
_				565					570					575	
_			580		Val			585					590		
		595		_	Thr		600					605			•
	610				Asn	615					620				
625					Val 630					635					640
тте	ASN	ATA	ASN	стА	Lys	Met	Asp	vaı	Tyr	GTÀ	ьys	Asp	val	άΤλ	Thr

645 650 Val Leu Asn Ser Ala Gly Thr Gln Thr Ile Tyr Ala Ser Ala Thr Ser 665 Asp Lys Ala Asn Ile Lys Gly Gly Lys Gln Thr Val Tyr Gly Leu, Ala 680 Thr Glu Ala Asn Ile Glu Ser Gly Glu Gln Ile Val Asp Gly Gly Ser 695 700 Thr Glu Lys Thr His Ile Asn Gly Gly Thr Gln Thr Val Gln Asn Tyr 715 710 Gly Lys Ala Ile Asn Thr Asp Ile Val Ser Gly Leu Gln Gln Ile Met 730 Ala Asn Gly Thr Ala Glu Gly Ser Ile Ile Asn Gly Gly Ser Gln Val 745 Val Asn Glu Gly Gly Leu Ala Glu Asn Ser Val Leu Asn Asp Gly Gly 760 Thr Leu Asp Val Arg Glu Lys Gly Ser Ala Thr Gly Ile Gln Gln Ser 775 780 Ser Gln Gly Ala Leu Val Ala Thr Thr Arg Ala Thr Arg Val Thr Gly 790 795 Thr Arg Ala Asp Gly Val Ala Phe Ser Ile Glu Gln Gly Ala Ala Asn 805 810 Asn Ile Leu Leu Ala Asn Gly Gly Val Leu Thr Val Glu Ser Asp Thr 825 820 Ser Ser Asp Lys Thr Gln Val Asn Met Gly Gly Arg Glu Ile Val Lys 840 Thr Lys Ala Thr Ala Thr Gly Thr Thr Leu Thr Gly Gly Glu Gln Ile 855 860 Val Glu Gly Val Ala Asn Glu Thr Thr Ile Asn Asp Gly Gly Ile Gln 870 875 Thr Val Ser Ala Asn Gly Glu Ala Ile Lys Thr Lys Ile Asn Glu Gly 885 890 Gly Thr Leu Thr Val Asn Asp Asn Gly Lys Ala Thr Asp Ile Val Gln 900 905 Asn Ser Gly Ala Ala Leu Gln Thr Ser Thr Ala Asn Gly Ile Glu Ile 920 925 915 Ser Gly Thr His Gln Tyr Gly Thr Phe Ser Ile Ser Gly Asn Leu Ala 935 Thr Asn Met Leu Leu Glu Asn Gly Gly Asn Leu Leu Val Leu Ala Gly 955 950 Thr Glu Ala Arg Asp Ser Thr Val Gly Lys Gly Gly Ala Met Gln Asn 965 970 Leu Gly Gln Asp Ser Ala Thr Lys Val Asn Ser Gly Gly Gln Tyr Thr 980 985 Leu Gly Arg Ser Lys Asp Glu Phe Gln Ala Leu Ala Arg Ala Glu Asp 1000 1005 Leu Gln Val Ala Gly Gly Thr Ala Ile Val Tyr Ala Gly Thr Leu Ala 1015 Asp Ala Ser Val Ser Gly Ala Thr Gly Ser Leu Ser Leu Met Thr Pro 1035 1030 Arg Asp Asn Val Thr Pro Val Lys Leu Glu Gly Ala Val Arg Ile Thr 1050 1045 Asp Ser Ala Thr Leu Thr Leu Gly Asn Gly Val Asp Thr Thr Leu Ala 1065 1070 Asp Leu Thr Ala Ala Ser Arg Gly Ser Val Trp Leu Asn Ser Asn Asn 1080 1085 Ser Cys Ala Gly Thr Ser Asn Cys Glu Tyr Arg Val Asn Ser Leu Leu 1095 1100 Leu Asn Asp Gly Asp Val Tyr Leu Ser Ala Gln Thr Ala Ala Pro Ala 1110 1115 1120 Thr Thr Asn Gly Ile Tyr Asn Thr Leu Thr Thr Asn Glu Leu Ser Gly

	112	E .		1	130				1135	
Ser Gly Asn			ic Thr			Gly	Sor	Δra		
Ser Gry Asii		Leu n.	12 1111	1145	ar nra	Gry		1150		rop
01- 7 11-1	1140	n n	71-		1 7	Dho				17 n 1
Gln Leu Val		ASN A			TA WRU				rne	Val
1155			1160				1165		T	77_ 1
Gln Asp Thr	GIA ASI			Ser A	sp Asp			Thr	Leu	Val
1170			175			1180				
Lys Thr Gly	Gly Gly	_	la Ser	Phe T			Asn	Thr	Gly	
1185		1190			1195					1200
Phe Val Asp	Leu Gly	Thr T	yr Glu			Lys	Ser	qeA	Gly	Asn
	120				210				1215	
Ser Asn Trp	Asn Leu	Thr A	sn Asp	Val L	ys Pro	Asn	Pro	Asp	Pro	Ile
_	1220			1225				1230)	
Pro Asn Pro	Lys Pro	Asp P	ro Lys	Pro A	sp Pro	Lys	Pro	Asp	Pro	Asn
123	-	-	1240		-		1245			
Pro Lys Pro		Thr P	ro Asp	Pro T	hr Pro	Thr	Pro	Val	Pro	Glu
1250	•		255			1260				
Lys Arg Ile	Thr Pro			Ala V	al Leu			Ala	Ala	Thr
1265		1270			1275					1280
Leu Pro Leu	Val Phe		la Glu	Leu A			Ara	Glu	Ara	
Dea tro Dea	128	_			290		9		1295	
Asn Ile Met			ro His	_		Val	Trp	Glv		
ASH THE MCC	1300	001		1305				1310		
Tyr Asn Thr		Aen W	al Thr		en Ala	Glu		-		Glu
191 ASII 1III 131!	-	Mail V	1320		op ma		1325		LIIC	OIG
Gln Thr Leu		Mot T			la Acn				Aco	Tlo
	Int Gry			GIY I	Te vsh	1340		ASII	nsp	116
1330	71- Mb-		335	71- D	ho Mot			C ~ ~	uio	802
Pro Glu Gly	iie inr		en era	Ald P			тĀт	ser	птэ	
1345		1350		n: - c	1355		C1	C	m	1360
His Ile Gly			TA GIA			Vai	GIY	ser	1375	
	136				.370	63	nh -	m		
Leu Gly Gly	-	Ser T	rp Giu		itu Ser	GTÄ	Pne	1390		Asp
	1380		m.	1385		17-1	7 1 <u>-</u>			M-+
GIV Val Val					er asn	vaı	Ата	GIV		IVIPIT
-	Lys Leu	Asn A							гу	
139	5		1400)			1405			
1399 Ser Ser Gly	5	Ala A	1400 sn Gly)		Ser	1405 Asn			
1399 Ser Ser Gly 1410	Gly Ala	Ala A 1	1400 sn Gly 415) Ser T	yr His	Ser 1420	1405 Asn	Gly	Leu	Gly
1399 Ser Ser Gly	Gly Ala	Ala A 1 Gly M	1400 sn Gly 415) Ser T	yr His	Ser 1420 Gly	1405 Asn	Gly	Leu	Gly Leu
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Ser Ser Gly 1410 Gly His Ile 1425 Thr Pro Tyr His Leu Ser	Gly Ala Glu Thr Ala Ser 144 Asn Gly 1460	Ala A 1 Gly M 1430 Leu T 5 Met L	1400 sn Gly 415 et Arg hr Gly ys Ser	Ser T Phe T Phe T Lys S 1465	Cyr His Chr Asp 1435 Chr Ala 450 Ger Val	Ser 1420 Gly Asp	1405 Asn Asn Asn Thr	Gly Trp Pro Arg 1470	Leu Asn Glu 1455 Ser	Gly Leu 1440 Tyr Ile
1399 Ser Ser Gly 1410 Gly His Ile 1425 Thr Pro Tyr	Gly Ala Glu Thr Ala Ser 144 Asn Gly 1460	Ala A 1 Gly M 1430 Leu T 5 Met L	1400 sn Gly 415 et Arg hr Gly ys Ser hr Leu	Ser T Phe T Phe T Lys S 1465 Ser T	Cyr His Chr Asp 1435 Chr Ala 450 Ger Val	Ser 1420 Gly Asp	1405 Asn Asn Asn Thr	Gly Trp Pro Arg 1470 Leu	Leu Asn Glu 1455 Ser	Gly Leu 1440 Tyr Ile
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Ser Ser Gly 1410 Gly His Ile 1425 Thr Pro Tyr His Leu Ser Tyr Arg Glu 147 Gly Met Glu 1490 Val Asp Asp 1505 Tyr Leu Ser Phe Ser Ser Ala Gly Val	Gly Ala Glu Thr Ala Ser 144 Asn Gly 1460 Leu Gly Val Glu Asn Arg Gly Arg 152 Thr Leu 1540 Glu Ser	Ala A 1 Gly M 1430 Leu T 5 Met L Ala T Pro T 1 Val L 1510 Arg G 5 Ser G	1400 sn Gly 415 et Arg hr Gly ys Ser hr Leu 1480 rp Leu 495 ys Val lly Ile lly His	Phe T Phe T Lys S 1465 Ser T Lys A Asn S Tyr G 1545 Ala V	Cyr His Thr Asp 1435 Thr Ala 450 Ger Val Cyr Asn Ala Ala Ser Asp 1515 Sin Ala 1530 Gly Val	Ser 1420 Gly Asp Asp Met Val 1500 Gly Gly Gly	1405 Asn Asn Asn Thr Arg 1485 Arg Asn Ile Tyr	Gly Trp Pro Arg 1470 Leu Lys Phe Lys Ser 1550 Asn	Leu Asn Glu 1455 Ser Gly Glu Val Ala 1535 His	Gly Leu 1440 Tyr Ile Asn Phe Asn 1520 Ser

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345
Val Pro Gly Ile Arg Pro Gly Glu Gln Thr Ala Lys Tyr Ile Asp Lys
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                                  365
Val Met Thr Arg Leu Thr Leu Val Gly Ala Leu Tyr Ile Thr Phe Ile
            375
                                     380
Cys Leu Ile Pro Glu Phe Met Arg Asp Ala Met Lys Val Pro Phe Tyr
        390
                                     395
Phe Gly Gly Thr Ser Leu Leu Ile Val Val Val Ile Met Asp Phe
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Met Ala Gln Val Gln Thr Leu Met Met Ser Ser Gln Tyr Glu Ser Ala
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Leu Lys Lys Ala Asn Leu Lys Gly Tyr Gly Arg
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Gly Phe Glu Gly Gly Gln Met Pro Leu Tyr Arg Arg Leu Pro Lys Phe
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Gly Phe Thr Ser Arg Lys Ala Ala Ile Thr Ala Glu Ile Arg Leu Ser
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Asp Leu Ala Lys Val Glu Gly Gly Val Val Asp Leu Asn Thr Leu Lys
              85
                                 90
Ala Ala Asn Ile Ile Gly Ile Gln Ile Glu Phe Ala Lys Val Ile Leu
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Ala Gly Glu Val Thr Thr Pro Val Thr Val Arg Gly Leu Arg Val Thr
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Gly His Thr Val Glu Arg Glu Asp Thr Pro Ala Ile Arg Gly Met Ile
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Asn Ala Val Ser Phe Met Val Lys Val Glu Glu
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Phe Thr Ala Leu Thr Val Val Gly Asp Gly Asn Gly Arg Val Gly Phe
                            40
Gly Tyr Gly Lys Ala Arg Glu Val Pro Ala Ala Ile Gln Lys Ala Met
                        55
Glu Lys Ala Arg Arg Asn Met Ile Asn Val Ala Leu Asn Asn Gly Thr
Leu Gln His Pro Val Lys Gly Val His Thr Gly Ser Arg Val Phe Met
                                   90
Gln Pro Ala Ser Glu Gly Thr Gly Ile Ile Ala Gly Gly Ala Met Arg
                               105
Ala Val Leu Glu Val Ala Gly Val His Asn Val Leu Ala Lys Ala Tyr
                            120
       115
Gly Ser Thr Asn Pro Ile Asn Val Val Arg Ala Thr Ile Asp Gly Leu
Glu Asn Met Asn Ser Pro Glu Met Val Ala Ala Lys Arg Gly Lys Ser
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                                       155
Val Glu Glu Ile Leu Gly Lys
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Lys Leu Gln Glu Leu Gly Ala Thr Arg Leu Val Val His Arg Thr Pro
Arg His Ile Tyr Ala Gln Val Ile Ala Pro Asn Gly Ser Glu Val Leu
       35
                           40
Val Ala Ala Ser Thr Val Glu Lys Ala Ile Ala Glu Gln Leu Lys Tyr
                        55
Thr Gly Asn Lys Asp Ala Ala Ala Ala Val Gly Lys Ala Val Ala Glu
Arg Ala Leu Glu Lys Gly Ile Lys Asp Val Ser Phe Asp Arg Ser Gly
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Phe Gln Tyr His Gly Arg Val Gln Ala Leu Ala Asp Ala Ala Arg Glu
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Ala Gly Leu Gln Phe
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Leu Thr Arg Thr Leu Asn Asp Ala Val Glu Val Lys His Ala Asp Asn
                           40
Thr Leu Thr Phe Gly Pro Arg Asp Gly Tyr Ala Asp Gly Trp Ala Gln
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Glu Gly Phe Thr Lys Lys Leu Gln Leu Val Gly Val Gly Tyr Arg Ala
Ala Val Lys Gly Asn Val Ile Asn Leu Ser Leu Gly Phe Ser His Pro
                       105
           100
Val Asp His Gln Leu Pro Ala Gly Ile Thr Ala Glu Cys Pro Thr Gln
                         120
                                            125
Thr Glu Ile Val Leu Lys Gly Ala Asp Lys Gln Val Ile Gly Gln Val
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Ala Ala Asp Leu Arg Ala Tyr Arg Arg Pro Glu Pro Tyr Lys Gly Lys
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Gly Val Arg Tyr Ala Asp Glu Val Val Arg Thr Lys Glu Ala Lys Lys
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Lys Val Ala Ile Ala Asn Val Leu Lys Glu Glu Gly Phe Ile Glu Asp
                           40
Phe Lys Val Glu Gly Asp Thr Lys Pro Glu Leu Glu Leu Thr Leu Lys
                       55
Tyr Phe Gln Gly Lys Ala Val Val Glu Ser Ile Gln Arg Val Ser Arg
                   70
Pro Gly Leu Arg Ile Tyr Lys Arg Lys Asp Glu Leu Pro Lys Val Met
              85
                                  90
Ala Gly Leu Gly Ile Ala Val Val Ser Thr Ser Lys Gly Val Met Thr
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Val Ala
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           20
                               25
Asp Val Asn Ala Ser Asp Glu Asp Arg Trp Asn Ala Val Leu Lys Leu
                           40
Gln Thr Leu Pro Arg Asp Ser Ser Pro Ser Arg Gln Arg Asn Arg Cys
                       55
Arg Gln Thr Gly Arg Pro His Gly Phe Leu Arg Lys Phe Gly Leu Ser
Arg Ile Lys Val Arg Glu Ala Ala Met Arg Gly Glu Ile Pro Gly Leu
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Ser Ala Gly Ile Asn Ala Ala Ser Pro Asn Lys Glu Leu Ala Lys Glu
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Phe Leu Glu Asn Tyr Leu Leu Thr Asp Glu Gly Leu Glu Ala Val Asn
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                                       315
Lys Asp Lys Pro Leu Gly Ala Val Ala Leu Lys Ser Tyr Glu Glu Glu
                                   330
Leu Ala Lys Asp Pro Arg Ile Ala Ala Thr Met Glu Asn Ala Gln Lys
                               345
Gly Glu Ile Met Pro Asn Ile Pro Gln Met Ser Ala Phe Trp Tyr Ala
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Glu Ala Leu Lys Asp Ala Gln Thr Arg Ile Thr Lys
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Leu Met Tyr Ala Gln Gly Glu Tyr Leu Phe Ala Ile Thr Thr Leu Ile
                           40
Leu Ser Ser Ala Gly Leu Tyr Ile Phe Ala Asn Arg Lys Ala Tyr Ala
Trp Arg Tyr Val Tyr Pro Gly Met Ala Gly Met Gly Leu Phe Val Leu
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Phe Pro Leu Val Cys Thr Ile Ala Ile Ala Phe Thr Asn Tyr Ser Ser
                                  90
              8.5
Thr Asn Gln Leu Thr Phe Glu Arg Ala Gln Glu Val Leu Leu Asp Arg
                              105
Ser Trp Gln Ala Gly Lys Thr Tyr Asn Phe Gly Leu Tyr Pro Ala Gly
                          120
Asp Glu Trp Gln Leu Ala Leu Ser Asp Gly Glu Thr Gly Lys Asn Tyr
             135
                                          140
Leu Ser Asp Ala Phe Lys Phe Gly Gly Glu Gln Lys Leu Gln Leu Lys
                150
                                      155
Glu Thr Thr Ala Gln Pro Glu Gly Glu Arg Ala Asn Leu Arg Val Ile
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Thr Gln Asn Arg Gln Ala Leu Ser Asp Ile Thr Ala Ile Leu Pro Asp
           180
                               185
Gly Asn Lys Val Met Met Ser Ser Leu Arg Gln Phe Ser Gly Thr Gln
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Pro Leu Tyr Thr Leu Asp Gly Asp Gly Thr Leu Thr Asn Asn Gln Ser
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Gly Val Lys Tyr Arg Pro Asn Asn Gln Ile Gly Phe Tyr Gln Ser Ile
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Thr Ala Asp Gly Asn Trp Gly Asp Glu Lys Leu Ser Pro Gly Tyr Thr
              245
                                   250
Val Thr Thr Gly Trp Lys Asn Phe Thr Arg Val Phe Thr Asp Glu Gly
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Ile Gln Lys Pro Phe Leu Ala Ile Phe Val Trp Thr Val Val Phe Ser
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Leu Ile Thr Val Phe Leu Thr Val Ala Val Gly Met Val Leu Ala Cys
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                                           300
Leu Val Gln Trp Glu Ala Leu Arg Gly Lys Ala Val Tyr Arg Val Leu
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Leu Ile Leu Pro Tyr Ala Val Pro Ser Phe Ile Ser Ile Leu Ile Phe
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Lys Gly Leu Phe Asn Gln Ser Phe Gly Glu Ile Asn Met Met Leu Ser
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Ala Leu Phe Gly Val Lys Pro Ala Trp Phe Ser Asp Pro Thr Thr Ala
                           360
Arg Thr Met Leu Ile Ile Val Asn Thr Trp Leu Gly Tyr Pro Tyr Met
                       375
                                           380
Met Ile Leu Cys Met Gly Leu Leu Lys Ala Ile Pro Asp Asp Leu Tyr
                   390
                                       395
Glu Ala Ser Ala Met Asp Gly Ala Gly Pro Phe Gln Asn Phe Phe Lys
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Ile Thr Leu Pro Leu Leu Ile Lys Pro Leu Thr Pro Leu Met Ile Ala
                               425
Ser Phe Ala Phe Asn Phe Asn Asn Phe Val Leu Ile Gln Leu Leu Thr
                           440
Asn Gly Gly Pro Asp Arg Leu Gly Thr Thr Thr Pro Ala Gly Tyr Thr
                       455
                                           460
Asp Leu Leu Val Asn Tyr Thr Tyr Arg Ile Ala Phe Glu Gly Gly
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Gly Gln Asp Phe Gly Leu Ala Ala Ala Ile Ala Thr Leu Ile Phe Leu
              485
                                  490
Leu Val Gly Ala Leu Ala Ile Val Asn Leu Lys Ala Thr Arg Met Lys
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Phe Asp
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<210> 327

<211> 296

<212> PRT

<213> Escherichia coli

<400> 327

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Pro Leu Ser Val Pro Ile Leu Ala Val Phe Ile Leu Ser Phe Ile 215 Ala Ala Ile Thr Glu Val Pro Val Ala Ser Leu Leu Leu Arg Asp Val 230 235 Asn Ser Tyr Thr Leu Ala Val Gly Met Gln Gln Tyr Leu Asn Pro Gln 245 250 Asn Tyr Leu Trp Gly Asp Phe Ala Ala Ala Ala Val Met Ser Ala Leu 260 265 Pro Ile Thr Ile Val Phe Leu Leu Ala Gln Arg Trp Leu Val Asn Gly 280 Leu Thr Ala Gly Gly Val Lys Gly <210> 328 <211> 673 <212> PRT <213> Escherichia coli <400> 328 Met Arg Leu Asn Pro Gly Gln Gln Ala Val Glu Phe Val Thr Gly 1 10 Pro Cys Leu Val Leu Ala Gly Ala Gly Ser Gly Lys Thr Arg Val Ile 25 Thr Asn Lys Ile Ala His Leu Ile Arg Gly Cys Gly Tyr Gln Ala Arg His Ile Ala Ala Val Thr Phe Thr Asn Lys Ala Ala Arg Glu Met Lys 55 60 Glu Arg Val Gly Gln Thr Leu Gly Arg Lys Glu Ala Arg Gly Leu Met 70 75 Ile Ser Thr Phe His Thr Leu Gly Leu Asp Ile Ile Lys Arg Glu Tyr 85 90 Ala Ala Leu Gly Met Lys Ala Asn Phe Ser Leu Phe Asp Asp Thr Asp 100 105 Gln Leu Ala Leu Leu Lys Glu Leu Thr Glu Gly Leu Ile Glu Asp Asp 120 Lys Val Leu Leu Gln Gln Leu Ile Ser Thr Ile Ser Asn Trp Lys Asn 135 140 Asp Leu Lys Thr Pro Ser Gln Ala Ala Ala Ser Ala Ile Gly Glu Arg 155 150 Asp Arg Ile Phe Ala His Cys Tyr Gly Leu Tyr Asp Ala His Leu Lys 170 Ala Cys Asn Val Leu Asp Phe Asp Asp Leu Ile Leu Leu Pro Thr Leu 185 Leu Leu Gln Ala Asn Glu Glu Val Arg Lys Arg Trp Gln Asn Lys Ile 200 Arg Tyr Leu Leu Val Asp Glu Tyr Gln Asp Thr Asn Thr Ser Gln Tyr 215 Glu Leu Val Lys Leu Leu Val Gly Ser Arg Ala Arg Phe Thr Val Val 230 235 Gly Asp Asp Asp Gln Ser Ile Tyr Ser Trp Arg Gly Ala Arg Pro Gln 250 245 Asn Leu Val Leu Leu Ser Gln Asp Phe Pro Ala Leu Lys Val Ile Lys 265 270 Leu Glu Gln Asn Tyr Arg Ser Ser Gly Arg Ile Leu Lys Ala Ala Asn 280 Ile Leu Ile Ala Asn Asn Pro His Val Phe Glu Lys Arg Leu Phe Ser 295 300 Glu Leu Gly Tyr Gly Ala Glu Leu Lys Val Leu Ser Ala Asn Asn Glu 310 315 Glu His Glu Ala Glu Arg Val Thr Gly Glu Leu Ile Ala His His Phe

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330
Val Asn Lys Thr Gln Tyr Lys Asp Tyr Ala Ile Leu Tyr Arg Gly Asn
                      345
          340
His Gln Ser Arg Val Phe Glu Lys Phe Leu Met Gln Asn Arg Ile Pro
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Tyr Lys Ile Ser Gly Gly Thr Ser Phe Phe Ser Arg Pro Glu Ile Lys
                    375
                                       380
Asp Leu Leu Ala Tyr Leu Arg Val Leu Thr Asn Pro Asp Asp Ser
         390
                          .395
Ala Phe Leu Arg Ile Val Asn Thr Pro Lys Arg Glu Ile Gly Pro Ala
        405 410
Thr Leu Lys Lys Leu Gly Glu Trp Ala Met Thr Arg Asn Lys Ser Met
                            425
         420
Phe Thr Ala Ser Phe Asp Met Gly Leu Ser Gln Thr Leu Ser Gly Arg
                         440
Gly Tyr Glu Ala Leu Thr Arg Phe Thr His Trp Leu Ala Glu Ile Gln
                     455
                                        460
Arg Leu Ala Glu Arg Glu Pro Ile Ala Ala Val Arg Asp Leu Ile His
                 470
                                    475
Gly Met Asp Tyr Glu Ser Trp Leu Tyr Glu Thr Ser Pro Ser Pro Lys
             485
                                490
Ala Ala Glu Met Arg Met Lys Asn Val Asn Gln Leu Phe Ser Trp Met
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Thr Glu Met Leu Glu Gly Ser Glu Leu Asp Glu Pro Met Thr Leu Thr
                       520
                                           525
Gln Val Val Thr Arg Phe Thr Leu Arg Asp Met Met Glu Arg Gly Glu
                    535
                                        540
Ser Glu Glu Glu Leu Asp Gln Val Gln Leu Met Thr Leu His Ala Ser
                                    555
                 550
Lys Gly Leu Glu Phe Pro Tyr Val Tyr Met Val Gly Met Glu Gly
                                570
              565
Phe Leu Pro His Gln Ser Ser Ile Asp Glu Asp Asn Ile Asp Glu Glu
          580
                            585
Arg Arg Leu Ala Tyr Val Gly Ile Thr Arg Ala Gln Lys Glu Leu Thr
                         600
Phe Thr Leu Cys Lys Glu Arg Arg Gln Tyr Gly Glu Leu Val Arg Pro
                                       620
                     615
Glu Pro Ser Arg Phe Leu Leu Glu Leu Pro Gln Asp Asp Leu Ile Trp
              630
                         635
Glu Gln Glu Arg Lys Val Val Ser Ala Glu Glu Arg Met Gln Lys Gly
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Gln Ser His Leu Ala Asn Leu Lys Ala Met Met Ala Ala Lys Arg Gly
Lys
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<210> 329

<211> 403

<212> PRT

<213> Escherichia coli

<400> 329

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 Tyr
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 Gln
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 Ser
 Gln
 Thr
 Gln

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 Ser
 Gln
 Thr
 Phe
 Ala
 Glu
 Lys
 Phe
 Thr
 Val
 Thr
 Glu
 Glu
 Leu
 Leu
 Leu
 Leu
 Ser
 Gly
 Asp
 Glu
 Glu
 Ser
 Ile
 Glu
 Glu
 Ser
 Ile
 Glu
 Ser
 Ile
 Glu
 Ala
 Leu
 Gly
 Tyr
 Asp
 Lys
 Phe
 Gly
 Lys
 Glu
 Ala

 50
 Ile
 Ala
 Ser
 Ile
 Gly
 Tyr
 Asp
 Lys
 Phe
 Gly
 Lys
 Glu
 Ala

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Glu Asp Ile Leu Tyr His Ile Val Arg Thr Pro Thr Asn Glu Thr Leu
                   70
                                       75
Ser Ile Ile Arg Leu Ile Lys Asn Ala Cys Leu Lys Leu Tyr Asn Leu
Ala His Ile Ala Thr Asn Ser Pro Leu Lys Ser His Asp Ser Asp Asp
                               105
Leu Leu Phe Lys Lys Leu Phe Ser Pro Ser Lys Leu Met Thr Ile Ile
                           120
Gly Asp Glu Ile Pro Leu Ile Ser Glu Lys Gln Ser Leu Ser Lys Val
                    135
Leu Leu Asn Asp Glu Asn Asn Glu Leu Ser Asp Gly Thr Asn Phe Trp
                  150
Asp Lys Asn Arg Gln Leu Thr Thr Asp Glu Ile Ala Cys Tyr Leu Gln
              165
                                  170
Lys Ile Ala Ala Asn Ala Lys Asn Thr Gln Val Asn Tyr Pro Thr Gly
                              185
          180
Leu Tyr Val Pro Tyr Ser Thr Arg Thr His Leu Glu Asp Ala Leu Asn
                           200
       195
Glu Asn Ile Lys Ser Asp Pro Ser Trp Pro Asn Glu Val Gln Leu Phe
                       215
                                           220
Pro Ile Asn Thr Gly Gly His Trp Ile Leu Val Ser Leu Gln Lys Ile
                                       235
                   230
Val Asn Lys Lys Asn Asn Lys Leu Gln Ile Lys Cys Val Ile Phe Asn
                                   250
Ser Leu Arg Ala Leu Gly Tyr Asp Lys Glu Asn Ser Leu Lys Arg Val
                               265
                                                   270
Ile Asn Ser Phe Asn Ser Glu Leu Met Gly Glu Met Ser Asn Asn Asn
                           280
                                               285
Ile Lys Val His Leu Asn Glu Pro Glu Ile Ile Phe Leu His Ala Asp
                      295
                                           300
Leu Gln Gln Tyr Leu Ser Gln Ser Cys Gly Ala Phe Val Cys Met Ala
                                       315
                   310
Ala Gln Glu Val Ile Glu Gln Arg Glu Ser Asn Ser Asp Ser Ala Pro
               325
                                   330
Tyr Thr Leu Leu Lys Asn His Ala Asp Arg Phe Lys Lys Tyr Ser Ala
                               345
           340
Glu Glu Gln Tyr Glu Ile Asp Phe Gln His Arg Leu Ala Asn Arg Asn
                           360
Cys Tyr Leu Asp Lys Tyr Gly Asp Ala Asn Ile Asn His Tyr Tyr Arg
                       375
                                           380
Asn Leu Glu Ile Lys His Ser Gln Pro Lys Asn Arg Ala Ser Gly Lys
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Arg Val Ser
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<210> 330

<211> 296

<212> PRT

<213> Escherichia coli

<400> 330

 Met
 Phe
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 Tyr
 Leu
 Gln
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 Thr
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 Pro
 Gly
 Ile
 Ile
 Phe

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 Asn
 Leu
 Ile
 Ser
 Val
 Ile
 Gly
 Gly
 Phe
 Leu
 Leu
 Leu
 Ala
 Ser
 Lys
 Gly

 Ser
 Ile
 Asp
 Tyr
 Pro
 Leu
 Phe
 Ile
 Tyr
 Thr
 Leu
 Val
 Gly
 Val
 Ser
 Leu

 Val
 Val
 Ala
 Ser
 Gly
 Cys
 Val
 Phe
 Asn
 Asn
 Tyr
 Ile
 Asp
 Arg
 Arg
 Arg
 Thr
 Lys
 Asn
 Arg
 Val
 Leu
 Val
 Leu
 Val
 Leu
 Leu
 Val
 Leu
 Val
 Leu
 Val
 Leu
 L

```
70
Ile Ser Pro Ala Val Ser Leu Val Tyr Ala Thr Leu Leu Gly Ile Ala
              85
Gly Phe Met Leu Leu Trp Phe Gly Ala Asn Pro Leu Ala Cys Trp Leu
                              105
Gly Val Met Gly Phe Val Val Tyr Val Gly Val Tyr Ser Leu Tyr Met
                         120
Lys Arg His Ser Val Tyr Gly Thr Leu Ile Gly Ser Leu Ser Gly Ala
            135
                                         140
Ala Pro Pro Val Ile Gly Tyr Cys Ala Val Thr Gly Glu Phe Asp Ser
         150
                                     155
Gly Ala Ala Ile Leu Leu Ala Ile Phe Ser Leu Trp Gln Met Pro His
                                  170
Ser Tyr Ala Ile Ala Ile Phe Arg Phe Lys Asp Tyr Gln Ala Ala Asn
                               185
Ile Pro Val Leu Pro Val Val Lys Gly Ile Ser Val Ala Lys Asn His
                           200
Ile Thr Leu Tyr Ile Ile Ala Phe Ala Val Ala Thr Leu Met Leu Ser
                       215
                                          220
Leu Gly Gly Tyr Ala Gly Tyr Lys Tyr Leu Val Val Ala Ala Ala Val
                   230
                                     235
Ser Val Trp Trp Leu Gly Met Ala Leu Arg Gly Tyr Lys Val Ala Asp
                                 250
              245
Asp Arg Ile Trp Ala Arg Lys Leu Phe Gly Phe Ser Ile Ile Ala Ile
                           265
          260
Thr Ala Leu Ser Val Met Met Ser Val Asp Phe Met Val Pro Asp Ser
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                          280
His Thr Leu Leu Ala Ala Val Trp
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<211> 315
<212> PRT
<213> Escherichia coli
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Ala Gly Thr Val Leu Leu Ser Gly Cys Asn Ser Ala Leu Leu Asp Pro
                               25
Lys Gly Gln Ile Gly Leu Glu Gln Arg Ser Leu Ile Leu Thr Ala Phe
                          40
Gly Leu Met Leu Ile Val Val Ile Pro Ala Ile Leu Met Ala Val Gly
                      55
Phe Ala Trp Lys Tyr Arg Ala Ser Asn Lys Asp Ala Lys Tyr Ser Pro
                   70
                                      75
Asn Trp Ser His Ser Asn Lys Val Glu Ala Val Val Trp Thr Val Pro
                                  90
               85
Ile Leu Ile Ile Ile Phe Leu Ala Val Leu Thr Trp Lys Thr Thr His
                               105
           100
Ala Leu Glu Pro Ser Lys Pro Leu Ala His Asp Glu Lys Pro Ile Thr
                                              125
                          120
Ile Glu Val Val Ser Met Asp Trp Lys Trp Phe Phe Ile Tyr Pro Glu
                       135
                                         140
Gln Gly Ile Ala Thr Val Asn Glu Ile Ala Phe Pro Ala Asn Thr Pro
                                      155
                  150
Val Tyr Phe Lys Val Thr Ser Asn Ser Val Met Asn Ser Phe Phe Ile
                                 170
                                                      175
              165
Pro Arg Leu Gly Ser Gln Ile Tyr Ala Met Ala Gly Met Gln Thr Arg
                        . 185
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Leu His Leu Ile Ala Asn Glu Pro Gly Thr Tyr Asp Gly Ile Ser Ala 200 195 Ser Tyr Ser Gly Pro Gly Phe Ser Gly Met Lys Phe Lys Ala Ile Ala 215 220 Thr Pro Asp Arg Ala Ala Phe Asp Gln Trp Val Ala Lys Ala Lys Gln 230 235 Ser Pro Asn Thr Met Ser Asp Met Ala Ala Phe Glu Lys Leu Ala Ala 250 245 Pro Ser Glu Tyr Asn Gln Val Glu Tyr Phe Ser Asn Val Lys Pro Asp 265 Leu Phe Ala Asp Val Ile Asn Lys Phe Met Ala His Gly Lys Ser Met 280 Asp Met Thr Gln Pro Glu Gly Glu His Ser Ala His Glu Gly Met Glu 295 300 Gly Met Asp Met Ser His Ala Glu Ser Ala His <210> 332 <211> 663 <212> PRT <213> Escherichia coli <400> 332 Met Phe Gly Lys Leu Ser Leu Asp Ala Val Pro Phe His Glu Pro Ile 10 Val Met Val Thr Ile Ala Gly Ile Ile Leu Gly Gly Leu Ala Leu Val 25 Gly Leu Ile Thr Tyr Phe Gly Lys Trp Thr Tyr Leu Trp Lys Glu Trp 40 Leu Thr Ser Val Asp His Lys Arg Leu Gly Ile Met Tyr Ile Ile Val Ala Ile Val Met Leu Leu Arg Gly Phe Ala Asp Ala Ile Met Met Arg 70 Ser Gln Gln Ala Leu Ala Ser Ala Gly Glu Ala Gly Phe Leu Pro Pro 90 His His Tyr Asp Gln Ile Phe Thr Ala His Gly Val Ile Met Ile Phe 100 105 Phe Val Ala Met Pro Phe Val Ile Gly Leu Met Asn Leu Val Val Pro 120 Leu Gln Ile Gly Ala Arg Asp Val Ala Phe Pro Phe Leu Asn Asn Leu 135 140 Ser Phe Trp Phe Thr Val Val Gly Val Ile Leu Val Asn Val Ser Leu 155 150 Gly Val Gly Glu Phe Ala Gln Thr Gly Trp Leu Ala Tyr Pro Pro Leu 170 165 Ser Gly Ile Glu Tyr Ser Pro Gly Val Gly Val Asp Tyr Trp Ile Trp 185 190 Ser Leu Gln Leu Ser Gly Ile Gly Thr Thr Leu Thr Gly Ile Asn Phe 200 205 195 Phe Val Thr Ile Leu Lys Met Arg Ala Pro Gly Met Thr Met Phe Lys 215 220 Met Pro Val Phe Thr Trp Ala Ser Leu Cys Ala Asn Val Leu Ile Ile 235 230 Ala Ser Phe Pro Ile Leu Thr Val Thr Val Ala Leu Leu Thr Leu Asp 245 250 Arg Tyr Leu Gly Thr His Phe Phe Thr Asn Asp Met Gly Gly Asn Met 270 265 260 Met Met Tyr Ile Asn Leu Ile Trp Ala Trp Gly His Pro Glu Val Tyr 280 285 275 Ile Leu Ile Leu Pro Val Phe Gly Val Phe Ser Glu Ile Ala Ala Thr

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295
                                          300
Phe Ser Arg Lys Arg Leu Phe Gly Tyr Thr Ser Leu Val Trp Ala Thr
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                                     315
Val Cys Ile Thr Val Leu Ser Phe Ile Val Trp Leu His His Phe Phe
               325
                                  330
Thr Met Gly Ala Gly Ala Asn Val Asn Ala Phe Phe Gly Ile Thr Thr
           340
                             345
Met Ile Ile Ala Ile Pro Thr Gly Val Lys Ile Phe Asn Trp Leu Phe
                          360
Thr Met Tyr Gln Gly Arg Ile Val Phe His Ser Ala Met Leu Trp Thr
                       375
                                          380
Ile Gly Phe Ile Val Thr Phe Ser Val Gly Gly Met Thr Gly Val Leu
                   390
                                      395
Leu Ala Val Pro Gly Ala Asp Phe Val Leu His Asn Ser Leu Phe Leu
              405
                                   410
Ile Ala His Phe His Asn Val Ile Ile Gly Gly Val Val Phe Gly Cys
                              425
           420
Phe Ala Gly Met Thr Tyr Trp Trp Pro Lys Ala Phe Gly Phe Lys Leu
                         440
Asn Glu Thr Trp Gly Lys Arg Ala Phe Trp Phe Trp Ile Ile Gly Phe
                      455
                                          460
Phe Val Ala Phe Met Pro Leu Tyr Ala Leu Gly Phe Met Gly Met Thr
                  470
                                     475
Arg Arg Leu Ser Gln Gln Ile Asp Pro Gln Phe His Thr Met Leu Met
              485
                                  490
Ile Ala Ala Ser Gly Ala Val Leu Ile Ala Leu Gly Ile Leu Cys Leu
           500
                               505
Val Ile Gln Met Tyr Val Ser Ile Arg Asp Arg Asp Gln Asn Arg Asp
                          520
Leu Thr Gly Asp Pro Trp Gly Gly Arg Thr Leu Glu Trp Ala Thr Ser
                      535
                                         540
Ser Pro Pro Pro Phe Tyr Asn Phe Ala Val Val Pro His Val His Glu
                550
                            555
Arg Asp Ala Phe Trp Glu Met Lys Glu Lys Gly Glu Ala Tyr Lys Lys
            565
                     570
Pro Asp His Tyr Glu Glu Ile His Met Pro Lys Asn Ser Gly Ala Gly
                              585
Ile Val Ile Ala Ala Phe Ser Thr Ile Phe Gly Phe Ala Met Ile Trp
                        600
His Ile Trp Trp Leu Ala Ile Val Gly Phe Ala Gly Met Ile Ile Thr
                       615
Trp Ile Val Lys Ser Phe Asp Glu Asp Val Asp Tyr Tyr Val Pro Val
                   630
                                      635
Ala Glu Ile Glu Lys Leu Glu Asn Gln His Phe Asp Glu Ile Thr Lys
               645
                                   650
Ala Gly Leu Lys Asn Gly Asn
           660
<210> 333
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<212> PRT
<213> Escherichia coli
<400> 333
Met Ala Thr Asp Thr Leu Thr His Ala Thr Ala His Ala His Glu His
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Gly His His Asp Ala Gly Gly Thr Lys Ile Phe Gly Phe Trp Ile Tyr
                               25
Leu Met Ser Asp Cys Ile Leu Phe Ser Ile Leu Phe Ala Thr Tyr Ala
```

40

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Val Leu Val Asn Gly Thr Ala Gly Gly Pro Thr Gly Lys Asp Ile Phe
                       55
Glu Leu Pro Phe Val Leu Val Glu Thr Phe Leu Leu Phe Ser Ser
                                        75
Ile Thr Tyr Gly Met Ala Ala Ile Ala Met Tyr Lys Asn Asn Lys Ser
Gln Val Ile Ser Trp Leu Ala Leu Thr Trp Leu Phe Gly Ala Gly Phe
           100
                               105
Ile Gly Met Glu Ile Tyr Glu Phe His His Leu Ile Val Asn Gly Met
       115
                           120
Gly Pro Asp Arg Ser Gly Phe Leu Ser Ala Phe Phe Ala Leu Val Gly
                       135
                                           140
Thr His Gly Leu His Val Thr Ser Gly Leu Ile Trp Met Ala Val Leu
                   150
                                       155
Met Val Gln Ile Ala Arg Arg Gly Leu Thr Ser Thr Asn Arg Thr Arg
               165
                                   170
Ile Met Cys Leu Ser Leu Phe Trp His Phe Leu Asp Val Val Trp Ile
                               185
Cys Val Phe Thr Val Val Tyr Leu Met Gly Ala Met
                            200
<210> 334
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<212> PRT
<213> Escherichia coli
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Met Ser His Ser Thr Asp His Ser Gly Ala Ser His Gly Ser Val Lys
                                    10
Thr Tyr Met Thr Gly Phe Ile Leu Ser Ile Ile Leu Thr Val Ile Pro
                                25
Phe Trp Met Val Met Thr Gly Ala Ala Ser Pro Ala Val Ile Leu Gly
Thr Ile Leu Ala Met Ala Val Val Gln Val Leu Val His Leu Val Cys
Phe Leu His Met Asn Thr Lys Ser Asp Glu Gly Trp Asn Met Thr Ala
                   70
Phe Val Phe Thr Val Leu Ile Ile Ala Ile Leu Val Val Gly Ser Ile
Trp Ile Met Trp Asn Leu Asn Tyr Asn Met Met His
<210> 335
<211> 587
<212> PRT
<213> Escherichia coli
<400> 335
Met Gln Trp Gln Thr Lys Leu Pro Leu Ile Ala Ile Leu Arg Gly Ile
1
Thr Pro Asp Glu Ala Leu Ala His Val Gly Ala Val Ile Asp Ala Gly
                                25
           20
Phe Asp Ala Val Glu Ile Pro Leu Asn Ser Pro Gln Trp Glu Gln Ser
Ile Pro Ala Ile Val Asp Ala Tyr Gly Asp Lys Ala Leu Ile Gly Ala
Gly Thr Val Leu Lys Pro Glu Gln Val Asp Ala Leu Ala Arg Met Gly
                   70
                                        75
Cys Gln Leu Ile Val Thr Pro Asn Ile His Ser Glu Val Ile Arg Arg
               85
                                    90
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Ala Val Gly Tyr Gly Met Thr Val Cys Pro Gly Cys Ala Thr Ala Thr
          100 105
Glu Ala Phe Thr Ala Leu Glu Ala Gly Ala Ala Gly Ala Glu Asn Ile
                        120
Ser Val Ile Gly Phe Trp Ser Ala Ile His Gln Ser Val Lys Ser Gly
             135
                             140
Ile Ala Ile Gly His Arg Ser Leu Cys Arg Trp Arg Arg Asp Ala Glu
        150 155
Asn Leu Ala Gln Trp Ile Asp Ala Gly Cys Ala Gly Ala Gly Leu Gly
           165
                               170
Ser Asp Leu Tyr Arg Ala Gly Gln Ser Val Glu Arg Thr Ala Gln Gln
                            185
Ala Ala Ala Phe Val Lys Ala Tyr Arg Glu Ala Gly Ala Met Lys Ile
           200
Thr Lys Ile Thr Thr Tyr Arg Leu Pro Pro Arg Trp Met Phe Leu Lys
 210 215 220
Ile Glu Thr Asp Glu Gly Val Val Gly Trp Gly Glu Pro Val Ile Glu
                                 235
               230
Gly Arq Ala Arg Thr Val Glu Ala Ala Val His Glu Leu Gly Asp Tyr
             245
                               250
Leu Ile Gly Gln Asp Pro Ser Arg Ile Asn Asp Leu Trp Gln Val Met
                           265
          260
Tyr Arg Ala Gly Phe Tyr Arg Gly Gly Pro Ile Leu Met Ser Ala Ile
                         280
Ala Gly Ile Asp Gln Ala Leu Trp Asp Ile Lys Gly Lys Val Leu Asn
                     295
                                      300
Ala Pro Val Trp Gln Leu Met Gly Gly Leu Val Arg Asp Lys Ile Lys
        310
                                 315
Ala Tyr Ser Trp Val Gly Gly Asp Arg Pro Ala Asp Val Ile Asp Gly
                               330
             325
Ile Lys Thr Leu Arg Glu Ile Gly Phe Asp Thr Phe Lys Leu Asn Gly
                           345
Cys Glu Glu Leu Gly Leu Ile Asp Asn Ser Arg Ala Val Asp Ala Ala
                        360
Val Asn Thr Val Ala Gln Ile Arg Glu Ala Phe Gly Asn Gln Ile Glu
                             380
                    375
Phe Gly Leu Asp Phe His Gly Arg Val Ser Ala Pro Met Ala Lys Val
                         395
       390
Leu Ile Lys Glu Leu Glu Pro Tyr Arg Pro Leu Phe Ile Glu Glu Pro
             405
                               410
Val Leu Ala Glu Gln Ala Glu Tyr Tyr Pro Lys Leu Ala Ala Gln Thr
                            425
His Ile Pro Leu Ala Ala Gly Glu Arg Met Phe Ser Arg Phe Asp Phe
                         440
                                          445
Lys Arg Val Leu Glu Ala Gly Gly Ile Ser Ile Leu Gln Pro Asp Leu
                     455
                                       460
Ser His Ala Gly Gly Ile Thr Glu Cys Tyr Lys Ile Ala Gly Met Ala
                 470
                                   475
Glu Ala Tyr Asp Val Thr Leu Ala Pro His Cys Pro Leu Gly Pro Ile
                               490
Ala Leu Ala Ala Cys Leu His Ile Asp Phe Val Ser Tyr Asn Ala Val
                            505
          500
Leu Gln Glu Gln Ser Met Gly Ile His Tyr Asn Lys Gly Ala Glu Leu
                        520
                                           525
Leu Asp Phe Val Lys Asn Lys Glu Asp Phe Ser Met Val Gly Gly Phe
                    535
Phe Lys Pro Leu Thr Lys Pro Gly Leu Gly Val Glu Ile Asp Glu Ala
                                   555
Lys Val Ile Glu Phe Ser Lys Asn Ala Pro Asp Trp Arg Asn Pro Leu
              565
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Trp Arg His Glu Asp Asn Ser Val Ala Glu Trp <210> 336 <211> 292 <212> PRT <213> Escherichia coli <400> 336 Met Thr Ala Arg Tyr Ile Ala Ile Asp Trp Gly Ser Thr Asn Leu Arg Ala Trp Leu Tyr Gln Gly Asp His Cys Leu Glu Ser Arg Gln Ser Glu 25 Ala Gly Val Thr Arg Leu Asn Gly Lys Ser Pro Ala Ala Val Leu Ala 40 Glu Val Thr Thr Asp Trp Arg Glu Glu Lys Thr Pro Val Val Met Ala 55 Gly Met Val Gly Ser Asn Val Gly Trp Lys Val Ala Pro Tyr Leu Ser 70 Val Pro Ala Cys Phe Ser Ser Ile Gly Glu Gln Leu Thr Ser Val Gly 90 Asp Asn Ile Trp Ile Ile Pro Gly Leu Cys Val Ser His Asp Asn 105 His Asn Val Met Arg Gly Glu Glu Thr Gln Leu Ile Gly Ala Arg Ala 120 Leu Ala Pro Ser Ser Leu Tyr Val Met Pro Gly Thr His Cys Lys Trp 130 135 140 Val Gln Ala Asp Ser Gln Gln Ile Asn Asp Phe Arg Thr Val Met Thr 150 155 Gly Glu Leu His His Leu Leu Leu Asn His Ser Leu Ile Gly Ala Gly 170 165 Leu Pro Pro Gln Glu Asn Ser Ala Asp Ala Phe Thr Ala Gly Leu Glu 185 Arg Gly Leu Asn Thr Pro Ala Ile Leu Pro Gln Leu Phe Glu Val Arg 195 200 205 Ala Ser His Val Leu Gly Thr Leu Pro Arg Glu Gln Val Ser Glu Phe 215 220 Leu Ser Gly Leu Leu Ile Gly Ala Glu Val Ala Ser Met Arg Asp Tyr 230 Val Ala His Gln His Ala Ile Thr Leu Val Ala Gly Thr Ser Leu Thr 250 Ala Arg Tyr Gln Gln Ala Phe Gln Ala Met Gly Cys Asp Val Thr Ala 265 Val Ala Gly Asp Thr Ala Phe Gln Ala Gly Ile Arg Ser Ile Ala His Ala Val Ala Asn 290 <210> 337 <211> 128 <212> PRT <213> Escherichia coli <400> 337 Met Thr Leu Asn Lys Thr Asp Arg Ile Val Ile Thr Leu Gly Lys Gln 10 Ile Val His Gly Lys Tyr Val Pro Gly Ser Pro Leu Pro Ala Glu Ala 25 Glu Leu Cys Glu Glu Phe Ala Thr Ser Arg Asn Ile Ile Arg Glu Val

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Phe Arg Ser Leu Met Ala Lys Arg Leu Ile Glu Met Lys Arg Tyr Arg
                  55
Gly Ala Phe Val Ala Pro Arg Asn Gln Trp Asn Tyr Leu Asp Thr Asp
                 70
Val Leu Gln Trp Val Leu Glu Asn Asp Tyr Asp Pro Arg Leu Ile Ser
                                90
Ala Met Ser Glu Val Arg Asn Leu Val Glu Pro Ala Ile Ala Arg Trp
                      105 110
Glu Gln Ser Ala Arg Leu Pro Ala Ile Trp Arg Arg Leu Asn Arg Arg
       115 120
<210> 338
<211> 98
<212> PRT
<213> Escherichia coli
<400> 338
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1
Arg Tyr His Glu Ala Val Leu Gln Ser Val His Asn Pro Val Leu Gln
                             25
Gln Leu Ser Ile Ala Ile Ser Ser Leu Gln Arg Ala Val Phe Glu Arg
                                            45
                          40
Thr Trp Met Gly Asp Glu Ala Asn Met Pro Gln Thr Leu Gln Glu His
                                        60
                     55
Lys Ala Leu Phe Asp Ala Ile Arg His Gln Asp Gly Asp Ala Ala Glu
65 70
Gln Ala Ala Leu Thr Met Ile Ala Ser Ser Thr Arg Arg Leu Lys Glu
                                 90
Ile Thr
<210> 339
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Ile Leu Lys Gln Ala Lys Gly Tyr Tyr Gly Ala Arg Ser Arg Val Tyr
                             25 .
  20
Arg Val Ala Phe Gln Ala Val Ile Lys Ala Gly Gln Tyr Ala Tyr Arg
                          40
                                            45
Asp Arg Arg Gln Arg Lys Arg Gln Phe Arg Gln Leu Trp Ile Ala Arg
                      55
Ile Asn Ala Ala Ala Arg Gln Asn Gly Ile Ser Tyr Ser Lys Phe Ile
                 70
Asn Gly Leu Lys Lys Ala Ser Val Glu Ile Asp Arg Lys Ile Leu Ala
              85
Asp Ile Ala Val Phe Asp Lys Val Ala Phe Thr Ala Leu Val Glu Lys
                             105
           100
Ala Lys Ala Ala Leu Ala
<210> 340
<211> 65
<212> PRT
<213> Escherichia coli
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Thr Gly Lys Gly Gly Phe Lys His Lys His Ala Asn Leu Arg His Ile
Leu Thr Lys Lys Ala Thr Lys Arg Lys Arg His Leu Arg Pro Lys Ala
                           40
Met Val Ser Lys Gly Asp Leu Gly Leu Val Ile Ala Cys Leu Pro Tyr
Ala
65
<210> 341
<211> 180
<212> PRT
<213> Escherichia coli
<400> 341
Met Lys Gly Gly Lys Arg Val Gln Thr Ala Arg Pro Asn Arg Ile Asn
Gly Glu Ile Arg Ala Gln Glu Val Arg Leu Thr Gly Leu Glu Gly Glu
           20
                               25
Gln Leu Gly Ile Val Ser Leu Arg Glu Ala Leu Glu Lys Ala Glu Glu
Ala Gly Val Asp Leu Val Glu Ile Ser Pro Asn Ala Glu Pro Pro Val
Cys Arg Ile Met Asp Tyr Gly Lys Phe Leu Tyr Glu Lys Ser Lys Ser
                    70
                                      75
Ser Lys Glu Gln Lys Lys Gln Lys Val Ile Gln Val Lys Glu Ile
               85
                                   90
Lys Phe Arg Pro Gly Thr Asp Glu Gly Asp Tyr Gln Val Lys Leu Arg
                               105
           100
                                                   110
Ser Leu Ile Arg Phe Leu Glu Glu Gly Asp Lys Ala Lys Ile Thr Leu
                            120
                                               125
Arg Phe Arg Gly Arg Glu Met Ala His Gln Gln Ile Gly Met Glu Val
                       135
                                           140
Leu Asn Arg Val Lys Asp Asp Leu Gln Glu Leu Ala Val Val Glu Ser
                   150
                                      155
Phe Pro Thr Lys Ile Glu Gly Arg Gln Met Ile Met Val Leu Ala Pro
Lys Lys Lys Gln
           180
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<211> 642
<212> PRT
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<400> 342
Met Pro Val Ile Thr Leu Pro Asp Gly Ser Gln Arg His Tyr Asp His
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Ala Val Ser Pro Met Asp Val Ala Leu Asp Ile Gly Pro Gly Leu Ala
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Lys Ala Cys Ile Ala Gly Arg Val Asn Gly Glu Leu Val Asp Ala Cys
Asp Leu Ile Glu Asn Asp Ala Gln Leu Ser Ile Ile Thr Ala Lys Asp
Glu Glu Gly Leu Glu Ile Ile Arg His Ser Cys Ala His Leu Leu Gly
                    70
                                      75
His Ala Ile Lys Gln Leu Trp Pro His Thr Lys Met Ala Ile Gly Pro
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90 85 Val Ile Asp Asn Gly Phe Tyr Tyr Asp Val Asp Leu Asp Arg Thr Leu 105 Thr Gln Glu Asp Val Glu Ala Leu Glu Lys Arg Met His Glu Leu Ala 125 120 Glu Lys Asn Tyr Asp Val Ile Lys Lys Lys Val Ser Trp His Glu Ala 140 135 Arg Glu Thr Phe Ala Asn Arg Gly Glu Ser Tyr Lys Val Ser Ile Leu 150 155 Asp Glu Asn Ile Ala His Asp Asp Lys Pro Gly Leu Tyr Phe His Glu 170 165 Glu Tyr Val Asp Met Cys Arg Gly Pro His Val Pro Asn Met Arg Phe 185 Cys His His Phe Lys Leu Met Lys Thr Ala Gly Ala Tyr Trp Arg Gly 200 Asp Ser Asn Asn Lys Met Leu Gln Arg Ile Tyr Gly Thr Ala Trp Ala 215 220 Asp Lys Lys Ala Leu Asn Ala Tyr Leu Gln Arg Leu Glu Glu Ala Ala 230 235 Lys Arg Asp His Arg Lys Ile Gly Lys Gln Leu Asp Leu Tyr His Met 250 245 Gln Glu Glu Ala Pro Gly Met Val Phe Trp His Asn Asp Gly Trp Thr 265 260 Ile Phe Arg Glu Leu Glu Val Phe Val Arg Ser Lys Leu Lys Glu Tyr 280 Gln Tyr Gln Glu Val Lys Gly Pro Phe Met Met Asp Arg Val Leu Trp 295 300 Glu Lys Thr Gly His Trp Asp Asn Tyr Lys Asp Ala Met Phe Thr Thr 315 310 Ser Ser Glu Asn Arg Glu Tyr Cys Ile Lys Pro Met Asn Cys Pro Gly 330 325 His Val Gln Ile Phe Asn Gln Gly Leu Lys Ser Tyr Arg Asp Leu Pro 345 Leu Arg Met Ala Glu Phe Gly Ser Cys His Arg Asn Glu Pro Ser Gly 360 Ser Leu His Gly Leu Met Arg Val Arg Gly Phe Thr Gln Asp Asp Ala 380 375 His Ile Phe Cys Thr Glu Glu Gln Ile Arg Asp Glu Val Asn Gly Cys 395 390 Ile Arg Leu Val Tyr Asp Met Tyr Ser Thr Phe Gly Phe Glu Lys Ile 410 405 Val Val Lys Leu Ser Thr Arg Pro Glu Lys Arg Ile Gly Ser Asp Glu 425 Met Trp Asp Arg Ala Glu Ala Asp Leu Ala Val Ala Leu Glu Glu Asn 440 Asn Ile Pro Phe Glu Tyr Gln Leu Gly Glu Gly Ala Phe Tyr Gly Pro 455 Lys Ile Glu Phe Thr Leu Tyr Asp Cys Leu Asp Arg Ala Trp Gln Cys 470 475 Gly Thr Val Gln Leu Asp Phe Ser Leu Pro Ser Arg Leu Ser Ala Ser 490 Tyr Val Gly Glu Asp Asn Glu Arg Lys Val Pro Val Met Ile His Arg - 505 Ala Ile Leu Gly Ser Met Glu Arg Phe Ile Gly Ile Leu Thr Glu Glu 520 Phe Ala Gly Phe Phe Pro Thr Trp Leu Ala Pro Val Gln Val Val Ile 535 540 Met Asn Ile Thr Asp Ser Gln Ser Glu Tyr Val Asn Glu Leu Thr Gln 555 550 Lys Leu Ser Asn Ala Gly Ile Arg Val Lys Ala Asp Leu Arg Asn Glu

570 565 Lys Ile Gly Phe Lys Ile Arg Glu His Thr Leu Arg Arg Val Pro Tyr 585 Met Leu Val Cys Gly Asp Lys Glu Val Glu Ser Gly Lys Val Ala Val 600 Arg Thr Arg Arg Gly Lys Asp Leu Gly Ser Met Asp Val Asn Glu Val 615 620 Ile Glu Lys Leu Gln Gln Glu Ile Arg Ser Arg Ser Leu Lys Gln Leu 630 Glu Glu <210> 343 <211> 330 <212> PRT <213> Escherichia coli <400> 343 Met Lys Ile Lys Asn Ile Leu Leu Thr Leu Cys Thr Ser Leu Leu Leu 10 Thr Asn Val Ala Ala His Ala Lys Glu Val Lys Ile Gly Met Ala Ile Asp Asp Leu Arg Leu Glu Arg Trp Gln Lys Asp Arg Asp Ile Phe Val Lys Lys Ala Glu Ser Leu Gly Ala Lys Val Phe Val Gln Ser Ala Asn 55 Gly Asn Glu Glu Thr Gln Met Ser Gln Ile Glu Asn Met Ile Asn Arg 70 75 Gly Val Asp Val Leu Val Ile Ile Pro Tyr Asn Gly Gln Val Leu Ser 90 85 Asn Val Val Lys Glu Ala Lys Gln Glu Gly Ile Lys Val Leu Ala Tyr 105 Asp Arg Met Ile Asn Asp Ala Asp Ile Asp Phe Tyr Ile Ser Phe Asp 120 Asn Glu Lys Val Gly Glu Leu Gln Ala Lys Ala Leu Val Asp Ile Val 140 135 Pro Gln Gly Asn Tyr Phe Leu Met Gly Gly Ser Pro Val Asp Asn Asn 150 155 Ala Lys Leu Phe Arg Ala Gly Gln Met Lys Val Leu Lys Pro Tyr Val 170 Asp Ser Gly Lys Ile Lys Val Val Gly Asp Gln Trp Val Asp Gly Trp 185 Leu Pro Glu Asn Ala Leu Lys Ile Met Glu Asn Ala Leu Thr Ala Asn 205 200 Asn Asn Lys Ile Asp Ala Val Val Ala Ser Asn Asp Ala Thr Ala Gly 215 220 Gly Ala Ile Gln Ala Leu Ser Ala Gln Gly Leu Ser Gly Lys Val Ala 230 235 Ile Ser Gly Gln Asp Ala Asp Leu Ala Gly Ile Lys Arg Ile Ala Ala 250 245 Gly Thr Gln Thr Met Thr Val Tyr Lys Pro Ile Thr Leu Leu Ala Asn 265 Thr Ala Ala Glu Ile Ala Val Glu Leu Gly Asn Gly Gln Glu Pro Lys 280 Ala Asp Thr Thr Leu Asn Asn Gly Leu Lys Asp Val Pro Ser Arg Leu 295 300 Leu Thr Pro Ile Asp Val Asn Lys Asn Asn Ile Lys Asp Thr Val Ile 310 315 Lys Asp Gly Phe His Lys Glu Ser Glu Leu 325

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<211> 55
<212> PRT
<213> Escherichia coli
<400> 344
Met Asn Lys Phe Ile Lys Val Ala Leu Val Gly Ala Val Leu Ala Thr
Leu Thr Ala Cys Thr Gly His Ile Glu Asn Arg Asp Lys Asn Cys Ser
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                               25
Tyr Asp Tyr Leu Leu His Pro Ala Ile Ser Ile Ser Lys Ile Ile Gly
      35
                       40
Gly Cys Gly Pro Thr Ala Gln
   50
<210> 345
<211> 462
<212> PRT
<213> Escherichia coli
<400> 345
Met Thr Ala Asn Ser Pro Leu Gln Arg Ile Gly Gln Glu Lys Gly Ile
Ala Met Gly Ser Gln Glu Leu Gln Arg Lys Leu Gly Phe Trp Ala Val
                               25
Leu Ala Ile Ala Val Gly Thr Thr Val Gly Ser Gly Ile Phe Val Ser
                           40
Val Gly Glu Val Ala Lys Ala Ala Gly Thr Pro Trp Leu Thr Val Leu
                      55
Ala Phe Val Ile Gly Gly Leu Ile Val Ile Pro Gln Met Cys Val Tyr
                  70
                                      75
Ala Glu Leu Ser Thr Ala Tyr Pro Glu Asn Gly Ala Asp Tyr Val Tyr
              85
                                  90
Leu Lys Asn Ala Gly Ser Arg Pro Leu Ala Phe Leu Ser Gly Trp Ala
                                                 110
                               105
Ser Phe Trp Ala Asn Asp Ala Pro Ser Leu Ser Ile Met Ala Leu Ala
                          120
                                              125
Ile Val Ser Asn Leu Gly Phe Leu Thr Pro Ile Asp Pro Leu Leu Gly
                                          140
                       135
Lys Phe Ile Ala Ala Gly Leu Ile Ile Ala Phe Met Leu Leu His Leu
                   150
                                       155
Arg Ser Val Glu Gly Gly Ala Ala Phe Gln Thr Leu Ile Thr Ile Ala
                                   170
               165
Lys Ile Ile Pro Phe Thr Ile Val Ile Gly Leu Gly Ile Phe Trp Phe
                               185
           180
Lys Ala Glu Asn Phe Ala Ala Pro Thr Thr Thr Ala Ile Gly Ala Thr
                          200
                                              205
Gly Ser Phe Met Ala Leu Leu Ala Gly Ile Ser Ala Thr Ser Trp Ser
                                          220
                      215
Tyr Thr Gly Met Ala Ser Ile Cys Tyr Met Thr Gly Glu Ile Lys Asn
                  230
                                       235
Pro Gly Lys Thr Met Pro Arg Ala Leu Ile Gly Ser Cys Leu Leu Val
                                   250
              245
Leu Val Leu Tyr Thr Leu Leu Ala Leu Val Ile Ser Gly Leu Met Pro
                              265
Phe Asp Lys Leu Ala Asn Ser Glu Thr Pro Ile Ser Asp Ala Leu Thr
        275 280
Trp Ile Pro Ala Leu Gly Ser Thr Ala Gly Ile Phe Val Ala Ile Thr
                       295
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Ala Met Ile Val Ile Leu Gly Ser Leu Ser Ser Cys Val Met Tyr Gln
                   310
                                       315
Pro Arg Leu Glu Tyr Ala Met Ala Lys Asp Asn Leu Phe Phe Lys Cys
               325
                                   330
Phe Gly His Val His Pro Lys Tyr Asn Thr Pro Asp Val Ser Ile Ile
           340
                              345
                                                 350
Leu Gln Gly Ala Leu Gly Ile Phe Phe Ile Phe Val Ser Asp Leu Thr
                          360
Ser Leu Leu Gly Tyr Phe Thr Leu Val Met Cys Phe Lys Asn Thr Leu
                      375
Thr Phe Gly Ser Ile Ile Trp Cys Arg Lys Arg Asp Asp Tyr Lys Pro
               390
                                   395
Leu Trp Arg Thr Pro Ala Phe Gly Leu Met Thr Thr Leu Ala Ile Ala
             405
                                  410
Ser Ser Leu Ile Leu Val Ala Ser Thr Phe Val Trp Ala Pro Ile Pro
           420
                               425
Gly Leu Ile Cys Ala Val Ile Val Ile Ala Thr Gly Leu Pro Ala Tyr
                           440
Ala Phe Trp Ala Lys Arg Ser Arg Gln Leu Asn Ala Leu Ser
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<212> PRT
<213> Escherichia coli
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Asp Phe Leu Val Thr Glu Asn Met Val Gln Glu Val Glu Lys Val Leu
Ser His Asp Val Pro Leu Val His Ala Ile Val Glu Glu Met Val Lys
                          40
Arg Asp Ile Asp Arg Ile Tyr Phe Val Ala Cys Gly Ser Pro Leu Asn
                    55
Ala Ala Gln Thr Ala Lys His Leu Ala Asp Arg Phe Ser Asp Leu Gln
Val Tyr Ala Ile Ser Gly Trp Glu Phe Cys Asp Asn Thr Pro Tyr Arg
                                 90
Leu Asp Asp Arg Cys Ala Val Ile Gly Val Ser Asp Tyr Gly Lys Thr
          100
                              105
Glu Glu Val Ile Lys Ala Leu Glu Leu Gly Arg Ala Cys Gly Ala Leu
                          120
                                             125
Thr Ala Ala Phe Thr Lys Arg Ala Asp Ser Pro Ile Thr Ser Ala Ala
                       135
                                          140
Glu Phe Ser Ile Asp Tyr Gln Ala Asp Cys Ile Trp Glu Ile His Leu
                   150
                                     155 .
Leu Leu Cys Tyr Ser Val Val Leu Glu Met Ile Thr Arg Leu Ala Pro
                                  170
               165
Asn Ala Glu Ile Gly Lys Ile Lys Asn Asp Leu Lys Gln Leu Pro Asn
                               185
Ala Leu Gly His Leu Val Arg Thr Trp Glu Glu Lys Gly Arg Gln Leu
                         200
                                              205
Gly Glu Leu Ala Ser Gln Trp Pro Met Ile Tyr Thr Val Ala Ala Gly
                                          220
                       215
Pro Leu Arg Pro Leu Gly Tyr Lys Glu Gly Ile Val Thr Leu Met Glu
                                      235
                  230
Phe Thr Trp Thr His Gly Cys Val Ile Glu Ser Gly Glu Phe Arg His
                                   250
              245
Gly Pro Leu Glu Ile Val Glu Pro Gly Val Pro Phe Leu Phe Leu Leu
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265
Gly Asn Asp Glu Ser Arg His Thr Thr Glu Arg Ala Ile Asn Phe Val
                        280
Lys Gln Arg Thr Asp Asn Val Ile Val Ile Asp Tyr Ala Glu Ile Ser
                      295
Gln Gly Leu His Pro Trp Leu Ala Pro Phe Leu Met Phe Val Pro Met
                  310
                              315
Glu Trp Leu Cys Tyr Tyr Leu Ser Ile Tyr Lys Asp His Asn Pro Asp
                               330
            325
Glu Arg Arg Tyr Tyr Gly Gly Leu Val Glu Tyr
<210> 347
<211> 149
<212> PRT
<213> Escherichia coli
<400> 347
Met Asn Ala Ala Ile Thr Val Val Trp Trp Asn Ile Asn Pro Ser Pro
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Gly Pro Ala Thr Gly Arg Ile Tyr Ala Arg Ser Tyr Pro Met Lys Thr
                              25
Gly Met Phe Thr Cys Gly His Gln Arg Leu Pro Ile Glu His Ala Phe
                          40
Arg Asp Ala Ser Glu Leu Gly Tyr Asp Gly Ile Glu Ile Trp Gly Gly
                      55
Arg Pro His Ala Phe Ala Pro Asp Leu Lys Ala Gly Gly Ile Lys Gln
                   70
Ile Lys Ala Leu Ala Gln Thr Tyr Gln Met Pro Ile Ile Gly Tyr Thr
                                  90
Pro Glu Thr Asn Gly Tyr Pro Tyr Asn Met Met Leu Gly Asp Glu His
                              105
Met Arg Arg Glu Ser Leu Asp Met Ile Lys Leu Ala Met Asp Met Ala
                          120
Lys Glu Met Asn Ala Gly Tyr Thr Leu Ile Ser Ala Gly Pro Arg Gly
                       135
Leu Ser His Ala Thr
145
<210> 348
<211> 127
<212> PRT
<213> Escherichia coli
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Met Arg Asp Ile Gln Met Val Leu Glu Arg Trp Gly Ala Trp Ala Ala
                                  10
Asn Asn His Glu Asp Val Thr Trp Ser Ser Ile Ala Ala Gly Phe Lys
                               25
Gly Leu Ile Thr Ser Lys Val Lys Ser Arg Pro Gln Cys Cys Asp Asp
                         40
Asp Ala Met Ile Ile Cys Gly Cys Met Ala Arg Leu Lys Lys Asn Asn
 50 · 55
Ser Asp Leu His Asp Leu Leu Val Asp Tyr Tyr Val Val Gly Met Thr
                                      75
Phe Met Ser Leu Ala Gly Lys His Cys Cys Ser Asp Gly Tyr Ile Gly
                                  90
Lys Arg Leu Gln Lys Ala Glu Gly Ile Ile Glu Gly Met Leu Met Ala
                              105
Leu Asp Ile Arg Leu Glu Met Asp Ile Val Val Asn Asn Ser Asn
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115 120 125

<210> 349

<211> 453

<212> PRT

<213> Escherichia coli

<400> 349

Met Phe Asp Asn Leu Thr Asp Arg Leu Ser Arg Thr Leu Arg Asn Ile 10 Ser Gly Arg Gly Arg Leu Thr Glu Asp Asn Val Lys Asp Thr Leu Arg Glu Val Arg Met Ala Leu Leu Glu Ala Asp Val Ala Leu Pro Val Val Arg Glu Phe Ile Asn Arg Val Lys Glu Lys Ala Val Gly His Glu Val 55 Asn Lys Ser Leu Thr Pro Gly Gln Glu Phe Val Lys Ile Val Arg Asn 70 75 Glu Leu Val Ala Ala Met Gly Glu Glu Asn Gln Thr Leu Asn Leu Ala Ala Gln Pro Pro Ala Val Leu Met Ala Gly Leu Gln Gly Ala Gly 105 Lys Thr Thr Ser Val Gly Lys Leu Gly Lys Phe Leu Arg Glu Lys His 120 Lys Lys Val Leu Val Val Ser Ala Asp Val Tyr Arg Pro Ala Ala 135 140 Ile Lys Gln Leu Glu Thr Leu Ala Glu Gln Val Gly Val Asp Phe Phe 150 155 Pro Ser Asp Val Gly Gln Lys Pro Val Asp Ile Val Asn Ala Ala Leu 170 165 Lys Glu Ala Lys Leu Lys Phe Tyr Asp Val Leu Leu Val Asp Thr Ala 185 Gly Arg Leu His Val Asp Glu Ala Met Met Asp Glu Ile Lys Gln Val 200 His Ala Ser Ile Asn Pro Val Glu Thr Leu Phe Val Val Asp Ala Met 215 220 Thr Gly Gln Asp Ala Ala Asn Thr Ala Lys Ala Phe Asn Glu Ala Leu 230 235 Pro Leu Thr Gly Val Val Leu Thr Lys Val Asp Gly Asp Ala Arg Gly 245 250 Gly Ala Ala Leu Ser Ile Arg His Ile Thr Gly Lys Pro Ile Lys Phe 265 Leu Gly Val Gly Glu Lys Thr Glu Ala Leu Glu Pro Phe His Pro Asp 280 Arg Ile Ala Ser Arg Ile Leu Gly Met Gly Asp Val Leu Ser Leu Ile 295 300 Glu Asp Ile Glu Ser Lys Val Asp Arg Ala Gln Ala Glu Lys Leu Ala 310 315 Ser Lys Leu Lys Lys Gly Asp Gly Phe Asp Leu Asn Asp Phe Leu Glu

Lys Leu Pro Gly Met Gly Gln Ile Pro Asp Asn Val Lys Ser Gln Met
355 360 365

Asp Asp Lys Val Leu Val Arg Met Glu Ala Ile Ile Asn Ser Met Thr
370 375 380

Met Lys Glu Arg Ala Lys Pro Glu Ile Ile Lys Gly Ser Arg Lys Arg
385 390 395 400

Gln Leu Arg Gln Met Lys Asn Met Gly Gly Met Ala Ser Leu Met Gly 340 345 350

325

Arg Ile Ala Ala Gly Cys Gly Met Gln Val Gln Asp Val Asn Arg Leu 405 410 415

330

Leu Lys Gln Phe Asp Asp Met Gln Arg Met Met Lys Lys Met Lys Lys 425 Gly Gly Met Ala Lys Met Met Arg Ser Met Lys Gly Met Met Pro Pro 440 Gly Phe Pro Gly Arg 450 <210> 350 <211> 577 <212> PRT <213> Escherichia coli <400> 350 Met Lys Gln Gln Ile Gln Leu Arg Arg Glu Val Asp Glu Thr Ala 10 Asp Leu Pro Ala Glu Leu Pro Pro Leu Leu Arg Arg Leu Tyr Ala Ser 20 Arg Gly Val Arg Ser Ala Gln Glu Leu Glu Arg Ser Val Lys Gly Met 40 Leu Pro Trp Gln Gln Leu Ser Gly Val Glu Lys Ala Val Glu Ile Leu 55 Tyr Asn Ala Phe Arg Glu Gly Thr Arg Ile Ile Val Val Gly Asp Phe Asp Ala Asp Gly Ala Thr Ser Thr Ala Leu Ser Val Leu Ala Met Arg 90 Ser Leu Gly Cys Ser Asn Ile Asp Tyr Leu Val Pro Asn Arg Phe Glu 100 105 Asp Gly Tyr Gly Leu Ser Pro Glu Val Val Asp Gln Ala His Ala Arg 120 115 Gly Ala Gln Leu Ile Val Thr Val Asp Asn Gly Ile Ser Ser His Ala 135 Gly Val Glu His Ala Arg Ser Leu Gly Ile Pro Val Ile Val Thr Asp 155 150 His His Leu Pro Gly Asp Thr Leu Pro Ala Ala Glu Ala Ile Ile Asn 170 165 Pro Asn Leu Arg Asp Cys Asn Phe Pro Ser Lys Ser Leu Ala Gly Val 185 180 Gly Val Ala Phe Tyr Leu Met Leu Ala Leu Arg Thr Phe Leu Arg Asp Gln Gly Trp Phe Asp Glu Arg Asn Ile Ala Ile Pro Asn Leu Ala Glu 215 Leu Leu Asp Leu Val Ala Leu Gly Thr Val Ala Asp Val Val Pro Leu 235 230 Asp Ala Asn Asn Arg Ile Leu Thr Trp Gln Gly Met Ser Arg Ile Arg 250 Ala Gly Lys Cys Arg Pro Gly Ile Lys Ala Leu Leu Glu Val Ala Asn 265 Arg Asp Ala Gln Lys Leu Ala Ala Ser Asp Leu Gly Phe Ala Leu Gly 280 Pro Arg Leu Asn Ala Ala Gly Arg Leu Asp Asp Met Ser Val Gly Val 300 295 Ala Leu Leu Cys Asp Asn Ile Gly Glu Ala Arg Val Leu Ala Asn 310 315 Glu Leu Asp Ala Leu Asn Gln Thr Arg Lys Glu Ile Glu Gln Gly Met 325 330 Gln Ile Glu Ala Leu Thr Leu Cys Glu Lys Leu Glu Arg Ser Arg Asp 345 350 Thr Leu Pro Gly Gly Leu Ala Met Tyr His Pro Glu Trp His Gln Gly 360 Val Val Gly Ile Leu Ala Ser Arg Ile Lys Glu Arg Phe His Arg Pro

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375
                                          380
Val Ile Ala Phe Ala Pro Ala Gly Asp Gly Thr Leu Lys Gly Ser Gly
                  390
                                      395
Arg Ser Ile Gln Gly Leu His Met Arg Asp Ala Leu Glu Arg Leu Asp
              405
                                  410
Thr Leu Tyr Pro Gly Met Met Leu Lys Phe Gly Gly His Ala Met Ala
           420
                             425
Ala Gly Leu Ser Leu Glu Glu Asp Lys Phe Lys Leu Phe Gln Gln Arg
                          440
       435
Phe Gly Glu Leu Val Thr Glu Trp Leu Asp Pro Ser Leu Leu Gln Gly
                      455
                                         460
Glu Val Val Ser Asp Gly Pro Leu Ser Pro Ala Glu Met Thr Met Glu
                           475
                 470
Val Ala Gln Leu Leu Arg Asp Ala Gly Pro Trp Gly Gln Met Phe Pro
             485
                                 490
Glu Pro Leu Phe Asp Gly His Phe Arg Leu Leu Gln Gln Arg Leu Val
                              505
Gly Glu Arg His Leu Lys Val Met Val Glu Pro Val Gly Gly Gly Pro
                          520
                                              525
Leu Leu Asp Gly Ile Ala Phe Asn Val Asp Thr Ala Leu Trp Pro Asp
                      535
                                         540
Asn Gly Val Arg Glu Val Gln Leu Ala Tyr Lys Leu Asp Ile Asn Glu
                   550
                                     555
Phe Arg Gly Asn Arg Ser Leu Gln Ile Ile Ile Asp Asn Ile Trp Pro
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                                  570
Ile
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<211> 236
<212> PRT
<213> Escherichia coli
<400> 351
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Phe Ala Gln Ala Asp Asp Ala Ala Ile Gln Gln Thr Leu Ala Lys Met
                              25
Gly Ile Lys Ser Ser Asp Ile Gln Pro Ala Pro Val Ala Gly Met Lys
      35
                          40
Thr Val Leu Thr Asn Ser Gly Val Leu Tyr Ile Thr Asp Asp Gly Lys
                                         60
                   55
His Ile Ile Gln Gly Pro Met Tyr Asp Val Ser Gly Thr Ala Pro Val
                                      75
                   70
Asn Val Thr Asn Lys Met Leu Leu Lys Gln Leu Asn Ala Leu Glu Lys
                                  90
Glu Met Ile Val Tyr Lys Ala Pro Gln Glu Lys His Val Ile Thr Val
                              105
           100
Phe Thr Asp Ile Thr Cys Gly Tyr Cys His Lys Leu His Glu Gln Met
                          120
                                             125
       115
Ala Asp Tyr Asn Ala Leu Gly Ile Thr Val Arg Tyr Leu Ala Phe Pro
                      135
                                          140
Arg Gln Gly Leu Asp Ser Asp Ala Glu Lys Glu Met Lys Ala Ile Trp
                  150
                                     155
Cys Ala Lys Asp Lys Asn Lys Ala Phe Asp Asp Val Met Ala Gly Lys
                                 170
              165
                                                     175
Ser Val Ala Pro Ala Ser Cys Asp Val Asp Ile Ala Asp His Tyr Ala
          180
                              185
Leu Gly Val Gln Leu Gly Val Ser Gly Thr Pro Ala Val Val Leu Ser
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200

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Asn Gly Thr Leu Val Pro Gly Tyr Gln Pro Pro Lys Glu Met Lys Glu
           215
Phe Leu Asp Glu His Gln Lys Met Thr Ser Gly Lys
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<210> 352
<211> 298
<212> PRT
<213> Escherichia coli
<400> 352
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Leu Glu Lys Asn Leu Ala Glu Asn Thr Leu Asn Ala Tyr Arg Arg Asp
                             25
Leu Ser Met Met Val Glu Trp Leu His His Arg Gly Leu Thr Leu Ala
                          40
Thr Ala Gln Ser Asp Asp Leu Gln Ala Leu Leu Ala Glu Arg Leu Glu
                           . 60
                     55
Gly Gly Tyr Lys Ala Thr Ser Ser Ala Arg Leu Leu Ser Ala Val Arg
                                    75
Arg Leu Phe Gln Tyr Leu Tyr Arg Glu Lys Phe Arg Glu Asp Asp Pro
                                90
              85
Ser Ala His Leu Ala Ser Pro Lys Leu Pro Gln Arg Leu Pro Lys Asp
                            105
          100
Leu Ser Glu Ala Gln Val Glu Arg Leu Leu Gln Ala Pro Leu Ile Asp
                         120
                                            125
Gln Pro Leu Glu Leu Arg Asp Lys Ala Met Leu Glu Val Leu Tyr Ala
                                        140
                      135
Thr Gly Leu Arg Val Ser Glu Leu Val Gly Leu Thr Met Ser Asp Ile
                  150
                                     155
Ser Leu Arg Gln Gly Val Val Arg Val Ile Gly Lys Gly Asn Lys Glu
              165
                                170
Arg Leu Val Pro Leu Gly Glu Glu Ala Val Tyr Trp Leu Glu Thr Tyr
                            185
          180
Leu Glu His Gly Arg Pro Trp Leu Leu Asn Gly Val Ser Ile Asp Val
                         200
Leu Phe Pro Ser Gln Arg Ala Gln Gln Met Thr Arg Gln Thr Phe Trp
                              220
          215
His Arg Ile Lys His Tyr Ala Val Leu Ala Gly Ile Asp Ser Glu Lys
                                  235
        230
Leu Ser Pro His Val Leu Arg His Ala Phe Ala Thr His Leu Leu Asn
                                 250
His Gly Ala Asp Leu Arg Val Val Gln Met Leu Leu Gly His Ser Asp
                             265
Leu Ser Thr Thr Gln Ile Tyr Thr His Val Ala Thr Glu Arg Leu Arg
                          280
Gln Leu His Gln Gln His His Pro Arg Ala
<210> 353
<211> 246
<212> PRT
<213> Escherichia coli
<400> 353
Met Phe Phe Asn Thr Lys His Thr Thr Ala Leu Cys Phe Val Thr Cys
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         5
Met Ala Phe Ser Ser Ser Ile Ala Asp Ile Val Ile Ser Gly Thr
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Arg Val Ile Tyr Lys Ser Asp Gln Lys Ser Val Asn Val Arg Leu Glu
                          40
Asn Lys Gly Asn Asn Pro Leu Leu Val Gln Ser Trp Leu Asp Thr Gly
Asp Asp Asn Ala Glu Pro Gly Ser Ile Thr Val Pro Phe Thr Ala Thr
                   70
Pro Pro Val Ser Arg Ile Asp Ala Lys Arg Gly Gln Thr Ile Lys Leu
Met Tyr Thr Ala Ser Thr Ser Leu Pro Lys Asp Arg Glu Ser Val Phe
                             105
        100
Trp Phe Asn Val Leu Glu Val Pro Pro Lys Pro Asp Ala Glu Lys Val
                         120
Ala Asn Gln Ser Leu Leu Gln Leu Ala Phe Arg Thr Arg Ile Lys Leu
          135
                                        140
Phe Tyr Arg Pro Asp Gly Leu Lys Gly Asn Pro Ser Glu Ala Pro Leu
                                   155
                  150
Ala Leu Lys Trp Phe Trp Ser Gly Ser Glu Gly Lys Ala Ser Leu Arg
              165
                                  170
Val Thr Asn Pro Thr Pro Tyr Tyr Val Ser Phe Ser Ser Gly Asp Leu
                              185
                                                190
Glu Ala Ser Gly Lys Arg Tyr Pro Ile Asp Val Lys Met Ile Ala Pro
                         200
Phe Ser Asp Glu Val Met Lys Val Asn Gly Leu Asn Gly Lys Ala Asn
                      215
Ser Ala Lys Val His Phe Tyr Ala Ile Asn Asp Phe Gly Gly Ala Ile
                            235
                 230
Glu Gly Asn Ala Arg Leu
               245
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<210> 354

<211> 865

<212> PRT

<213> Escherichia coli

<400> 354

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		195					200					205			
Gly	Ala 210	Trp	Arg	Leu	Arg	Ala 215		Gly	Asn	Tyr	Asn 220	Trp	Met	Thr	Asp
225					Asp 230					235					240
				245	Gln				250					255	
			260		Val			265					270		
	_	275			Pro		280					285			
_	290				Asn	295					300				
305		-			Thr 310					315					320
				325	Tyr				330					335	
			340		Arg			345					350		
		355			Gly		360					365			
	370				Ile	375					380				
385					Asn 390					395					400
				405	Tyr				410					415	
			420		Phe			425					430		
		435	_	_	Thr		440					445			
	450				Glu	455					460				
465					Asn 470					475					480
	-			485	His				490					495	
_			500		Met			505					510		
		515			Lys		520					525			
	530				Trp	535					540				
545					550					555					Ala 560
				565					570					575	Leu
			580					585					5 9 0		Thr
	_	595					600					605			Gly
	610					615					620				Arg
625		-			630					635			.•		Lys 640
_				645					650					655	
			660					665			•		670		Val
Ser	Leu	Ser	Thr	Asp	Gly	Gly	Phe	Val	Leu	His	Ser	Gly	Gly	Leu	Thr

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680
       675
Phe Ser Asn Asp Ser Phe Ser Asp Ser Asp Thr Leu Ala Val Val Gln
                      695
Ala Pro Gly Ala Gln Gly Ala Arg Ile Asn Tyr Gly Asn Ser Thr Ile
                  710
                                     715
Asp Arg Trp Gly Tyr Gly Val Thr Ser Ala Leu Ser Pro Tyr His Glu
               725
                                 730
Asn Arg Ile Ala Leu Asp Ile Asn Asp Leu Glu Asn Asp Val Glu Leu
                              745
Lys Ser Thr Ser Ala Val Ala Val Pro Arg Gln Gly Ser Val Val Phe
                760
Ala Asp Phe Glu Thr Val Gln Gly Gln Ser Ala Ile Met Asn Ile Thr
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Arg Ser Asp Gly Lys Asn Ile Pro Phe Ala Ala Asp Ile Tyr Asp Glu
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                                      795
Gln Gly Asn Val Ile Gly Asn Val Gly Gln Gly Gln Ala Phe Val
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Arg Gly Ile Glu Gln Gln Gly Asn Ile Ser Ile Lys Trp Leu Glu Gln
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           820
Ser Lys Pro Val Ser Cys Leu Ala His Tyr Gln Gln Ser Pro Glu Ala
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Gln
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Ser Thr Thr Glu Thr Thr Glu Pro Asp Arg Thr Leu Gln Leu Ser Ala
Glu Gln Ala Ala Arg Ile Arg Glu Met Thr Val Ile Thr Ser Ser Leu
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                                         60
Met Met Ser Leu Thr Val Asp Glu Ser Asp Leu Ser Val His Leu Val
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                                      75
Gly Arg Lys Ile Asn Lys Arg Glu Trp Ala Gly Asn Ala Ser Ala Trp
His Asp Thr Pro Ala Val Ala Arg Asp Leu Ser His Gly Leu Ser Phe
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Ala Glu Gln Val Val Ser Glu Ala His Ser Ala Ile Val Ile Leu Asp
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Ser Arg Gly Asn Ile Gln Arg Phe Asn Arg Leu Cys Glu Asp Tyr Thr
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                                          140
Gly Leu Lys Glu His Asp Val Ile Gly Gln Ser Val Phe Lys Leu Phe
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Met Ser Arg Arg Glu Ala Ala Ala Ser Arg Arg Asn Asn Arg Val Phe
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Phe Arg Ser Gly Asn Ala Tyr Glu Val Glu Leu Trp Ile Pro Thr Cys
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                                                 190
           180
Lys Gly Gln Arg Leu Phe Leu Phe Arg Asn Lys Phe Val His Ser Gly
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                                             205
Ser Gly Lys Asn Glu Ile Phe Leu Ile Cys Ser Gly Thr Asp Ile Thr
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PCT/US00/30950 WO 01/34810

Glu 225	Glu	Arg	Arg	Ala	Gln 230	Glu	Arg	Leu	Arg	Ile 235	Leu	Ala	Asn	Thr	Asp 240
	Ile	Thr	Gly		Pro	Asn	Arg	neA			Gln	Asp	Leu	Ile 255	
His	Ala	Ile		245 His	Ala	Asp	Asn		250 Lys	Val	Gly	Val			Leu
Asp	Leu		260 Asn	Phe	Lys	Lys		265 Asn	Asp	Ala	Tyr		270 His	Leu	Phe
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Gly	Asp 290	Gln	Leu	Leu	Arg	Asp 295	Val	Ser	Leu	Ala	Ile 300	Leu	Ser	Cys ·	Leu
Glu 305	His	Asp	Gln	Val	Leu 310	Ala	Arg	Pro	Gly	Gly 315	Asp	Glu	Phe	Leu	Val 320
Leu	Ala	Ser	Asn	Thr 325	Ser	Gln	Ser	Ala	Leu 330	Glu	Ala	Met	Ala	Ser 335	Arg
Ile	Leu	Thr	Arg 340	Leu	Arg	Leu	Pro	Phe 345	Arg	Ile	Gly	Leu	Ile 350	Glu	Val
Tyr	Thr	Ser 355		Ser	Val	Gly	Ile 360		Leu	Ser	Pro	Glu 365		Gly	Ser
Asp	Ser 370		Ala	Ile	Ile	Arg 375		Ala	Asp	Thr	Ala 380		Tyr	Thr	Ala
Lys 385		Gly	Gly	Arg	Gly 390		Phe	Cys	Val	Phe 395		Pro	Glu	Met	Asn 400
		**- 3	DL -	61		T		¥	7		3	T	7 ·	T	
	_			405	Tyr -				410					415	
			420		Leu			425					430		
-	-	435			Ser		440					445			
	450				Pro	455					460				
Ser	Glv	Leu	Ile	Val	Pro	Leu	Gly	Arg	Trp	Val	Ile	Leu	Asp	Val	Val
465	-				470		_	_	-	475			_		480
	Gln	Val	Ala	Lys	Trp	Arg	Asp	Lys	Gly	Ile	Asn	Leu	Arg	Val	Ala
** . 1	3	71 -	0	485	D	C1-	7	n1_	490	C1-	mb	T1.	Dho	495	71.0
val	ASI	ire	500	ATG	Arg	GIII	Leu	505	мър	GIII	1111	116	510	1111	Ата
Leu	Lys	Gln 515	Val	Leu	Gln	Glu	Leu 520	Asn	Phe	Glu	Tyr	Cys 525	Pro	Ile	Asp
Val	Glu 530	Leu	Thr	Glu	Ser	Cys 535	Leu	Ile	Glu	Asn	Asp 540	Glu	Leu	Ala	Leu
Ser		Ile	Gln	Gln	Phe	Ser	Gln	Leu	Gly		Gln	Val	His	Leu	
545					550					555					560
_				565	Tyr				570					575	
Ile	Asp	Ala	Ile 580	Lys	Leu	Asp	Gln	Val 585	Phe	Val	Arg	Asp	Ile 590	His	Lys
Gln	Pro	Val 595	Ser	Gln	Ser	Leu	Val 600	Arg	Ala	Ile	Val	Ala 605	Val	Ala	Gln
Ala	Leu 610	Asn	Leu	Gln	Val	Ile 615	Ala	Glu	Gly	Val	Glu 620	Ser	Ala	Lys	Glu
Asp 625		Phe	Leu	Thr	Lys 630	Asn	Gly	Ile	Asn	Glu 635	Arg	Gln	Gly	Phe	Leu 640
	7. T. C	T	D	Mot		λ 1 ~	17-1	N 3 -	Dha		A	η···	Фил	Luc	
rne	MIG	ոնջ	FEO	Met 645	Pro	WIG	val	. urq	650	GIU	ur d	тъ	+ A r	655	ary
Tyr	Leu	Lys	Arg 660	Ala	•					•					•
.0.5															

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<213> Escherichia coli

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Le	ı Ser	Ser	Ala	His	Glv	Tvr	Ile	Pro	Pro	Glu	Glu	Trp	Asp	Glu	Glv
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Gl	y Asn	Asp 195	Ser	Tyr	Phe	Phe	Ser 200	Glu	Leu	Ser	Gly	11e 205	Asn	Ile	Gly
Pr	210	Arg	Leu	Arg	Asn		Gly	Ser	Trp	Asn	Tyr 220	Phe	Arg	Gly	Asn
G1 22	y Tyr	His	Ser	Glu	Gln 230	Trp	Asn	Asn	Ile	Gly 235	Thr	Trp	Val	Gln	Arg 240
	a Ile	Ile	Pro	Leu 245	Lys	Ser	Glu	Leu	Val 250	Met	Gly	Asp	Gly	Asn 255	Thr
Gl	y Ser	Asp	Ile 260	Phe	Asp	Gly	Val	Gly 265	Phe	Arg	Gly	Val	Arg 270	Leu	Tyr
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Va	l Arg 290		Ile	Alá	Arg	Thr 295		Ala	Gln	Leu	Thr 300		Arg	Gln	Asn
G1 30	y Phe	Ile	Ile	Tyr	Gln 310		Tyr	Val	Ser	Pro 315		Ala	Phe	Glu	Ile 320
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Va	l Pro	Ile 355		Gln	Arg	Glu	Gly 360		Phe	Lys	Phe	Asp 365			Ala
Gl	y Asp 370		Arg	Ser	Gly	Asn 375		Gln	Gln	Ser	Ser 380		Phe	Phe	Phe
G1 38	n Gly	Thr	Ala	Leu	Gly 390		Leu	Pro	Gln	Glu 395		Thr	Ala	Tyr	Gly 400
	y Thr	Gln	Leu	Ser		Aen	Tur	Thr	Δla		T.en	Len.	Clu	T 011	C1
				405	AIG	ASII	ıyı	1111	410	1110	200	DCG	GIY	415	GLY
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Ar		Leu Gln	Gly 420	405 Asn	Trp	Gly	Ala	Val 425	410 Ser	Leu	Asp	Val	Thr 430	415 His	Ala
Ar Ar	g Asn	Leu Gln 435	Gly 420 Leu	405 Asn Ala	Trp Asp	Gly Ala	Ala Ser 440	Val 425 Arg	410 Ser His	Leu Glu	Asp Gly	Val Asp 445	Thr 430 Ser	415 His Ile	Ala Arg
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Ar Ar Ph Me	g Asn g Ser e Leu 450 t Gly	Leu Gln 435 Tyr	Gly 420 Leu Ala Arg	405 Asn Ala Lys Tyr	Trp Asp Ser Ser 470	Gly Ala Met 455 Thr	Ala Ser 440 Asn Gln	Val 425 Arg Thr	410 Ser His Phe	Leu Glu Gly Tyr 475	Asp Gly Thr 460 Thr	Val Asp 445 Asn Leu	Thr 430 Ser Phe Asp	415 His Ile Gln Asp	Ala Arg Leu Val 480
Ar Ar Ph Me 46 Al	g Asn g Ser e Leu 450 t Gly	Leu Gln 435 Tyr Tyr	Gly 420 Leu Ala Arg	405 Asn Ala Lys Tyr Met 485	Trp Asp Ser Ser 470 Glu	Gly Ala Met 455 Thr	Ala Ser 440 Asn Gln Tyr	Val 425 Arg Thr Gly	410 Ser His Phe Phe Tyr 490	Leu Glu Gly Tyr 475 Asp	Asp Gly Thr 460 Thr	Val Asp 445 Asn Leu Asp	Thr 430 Ser Phe Asp	415 His Ile Gln Asp Glu 495	Ala Arg Leu Val 480 His
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Arr Ph Me 46 Al Arr Ly	g Asn g Ser e Leu 450 t Gly a Tyr	Leu Gln 435 Tyr Tyr Arg Glu Arg 515	Gly 420 Leu Ala Arg Arg Pro 500 Leu	A05 Asn Ala Lys Tyr Met 485 Ile Gln	Trp Asp Ser Ser 470 Glu Ile Leu	Gly Ala Met 455 Thr Gly Val Asn	Ala Ser 440 Asn Gln Tyr Asn Val 520	Val 425 Arg Thr Gly Glu Tyr 505 Ser	410 Ser His Phe Phe Tyr 490 His	Leu Glu Gly Tyr 475 Asp Asn Ser	Asp Gly Thr 460 Thr Tyr Leu Leu	Val Asp 445 Asn Leu Asp Arg	Thr 430 Ser Phe Asp Gly Phe 510 Asp	415 His Ile Gln Asp Glu 495 Ser Phe	Ala Arg Leu Val 480 His Arg
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Arr Ph Me 46 Al Arr Ly Se 54	y Asn y Ser e Leu 450 c Gly a Tyr g Asp r Leu 530 r Asp	Leu Gln 435 Tyr Tyr Arg Glu Arg 515 Tyr	Gly 420 Leu Ala Arg Pro 500 Leu Ile	405 Asn Ala Lys Tyr Met 485 Ile Gln Ser	Trp Asp Ser 470 Glu Ile Leu Gly Gln 550	Gly Ala Met 455 Thr Gly Val Asn Thr 535 Val	Ala Ser 440 Asn Gln Tyr Asn Val 520 His	Val 425 Arg Thr Gly Glu Tyr 505 Ser Gln Tyr	410 Ser His Phe Phe Tyr 490 His Gln Lys	Leu Glu Gly Tyr 475 Asp Asn Ser Tyr	Asp Gly Thr 460 Thr Tyr Leu Leu Trp 540 Ser	Val Asp 445 Asn Leu Asp Arg Asn 525 Asn	Thr 430 Ser Phe Asp Gly Phe 510 Asp Thr	415 His Ile Gln Asp Glu 495 Ser Phe Ser Gly	Ala Arg Leu Val 480 His Arg Gly Asp Ile 560
Arr Ph Me 46 Al Arr Ly Se 54 Se	y Asn y Ser e Leu 450 c Gly a Tyr g Asp s Asp r Leu 530 r Asp	Leu Gln 435 Tyr Tyr Arg Glu Arg 515 Tyr Thr	Gly 420 Leu Ala Arg Pro 500 Leu Ile Trp	A05 Asn Ala Lys Tyr Met 485 Ile Gln Ser Tyr Ser 565	Trp Asp Ser 470 Glu Ile Leu Gly Gln 550 Phe	Gly Ala Met 455 Thr Gly Val Asn Thr 535 Val Ser	Ala Ser 440 Asn Gln Tyr Asn Val 520 His Gly Trp	Val 425 Arg Thr Gly Glu Tyr 505 Ser Gln Tyr	His Phe Phe Tyr 490 His Gln Lys Thr Glu 570	Leu Glu Gly Tyr 475 Asp Asn Ser Tyr Ser 555 Ser	Asp Gly Thr 460 Thr Tyr Leu Leu Trp 540 Ser Val	Val Asp 445 Asn Leu Asp Arg Arg Trp Gly	Thr 430 Ser Phe Asp Gly Phe 510 Asp Thr Val	415 His Ile Gln Asp Glu 495 Ser Phe Ser Gly Pro 575	Ala Arg Leu Val 480 His Arg Gly Asp Ile 560 Asp
Arr Ph Me 46 Al Arr Ly Se 54 Se As	y Asn y Ser e Leu 450 c Gly a Tyr g Asp s Asp r Leu 530 r Asp	Leu Gln 435 Tyr Tyr Arg Glu Arg 515 Tyr Thr Ser Arg	Gly 420 Leu Ala Arg Pro 500 Leu Ile Trp Leu Ile 580	A05 Asn Ala Lys Tyr Met 485 Ile Gln Ser Tyr Ser 565 Val	Trp Asp Ser 470 Glu Ile Leu Gly Gln 550 Phe	Gly Ala Met 455 Thr Gly Val Asn Thr 535 Val Ser Leu	Ala Ser 440 Asn Gln Tyr Asn Val 520 His Gly Trp Asn	Val 425 Arg Thr Gly Glu Tyr 505 Ser Gln Tyr Asn Val 585	His Phe Phe Tyr 490 His Gln Lys Thr Glu 570 Ser	Leu Glu Gly Tyr 475 Asp Asn Ser Tyr Ser 555 Ser Val	Asp Gly Thr 460 Thr Tyr Leu Leu Trp 540 Ser Val	Val Asp 445 Asn Leu Asp Arg Arg Cly Phe	Thr 430 Ser Phe Asp Gly Phe 510 Asp Thr Val Ile Asn 590	415 His Ile Gln Asp Glu 495 Ser Phe Ser Gly Pro 575 Val	Ala Arg Leu Val 480 His Arg Gly Asp Ile 560 Asp
Arr Ph Me 46 Al Arr Ly Se 54 Se Th	y Asn y Ser e Leu 450 c Gly f Tyr g Asp r Leu 530 r Asp r Tyr	Leu Gln 435 Tyr Tyr Arg Glu Arg 515 Tyr Thr Ser Arg Arg 595 Asn	Gly 420 Leu Ala Arg Pro 500 Leu Ile Trp Leu Ile 580 Arg	405 Asn Ala Lys Tyr Met 485 Ile Gln Ser Tyr Ser 565 Val	Trp Asp Ser 470 Glu Ile Leu Gly Gln 550 Phe Gly Thr	Gly Ala Met 455 Thr Gly Val Asn Thr 535 Val Ser Leu Arg	Ala Ser 440 Asn Gln Tyr Asn Val 520 His Gly Trp Asn Glu 600	Val 425 Arg Thr Gly Glu Tyr 505 Ser Gln Tyr Asn Val 585 Asn	His Phe Phe Tyr 490 His Gln Lys Thr Glu 570 Ser Ala	Leu Glu Gly Tyr 475 Asp Asn Ser Tyr Ser 555 Ser Val Leu	Asp Gly Thr 460 Thr Tyr Leu Leu Trp 540 Ser Val Pro Asp	Val Asp 445 Asn Leu Asp Arg Arg Gly Phe Arg 605	Thr 430 Ser Phe Asp Gly Phe 510 Asp Thr Val Ile Asn 590 Ala	415 His Ile Gln Asp Glu 495 Ser Phe Ser Gly Pro 575 Val	Ala Arg Leu Val 480 His Arg Gly Asp Ile 560 Asp Leu Ala
Arr Ph Me 46 Al Arr Ly Se 54 Se Th	y Asn y Ser e Leu 450 c Gly a Tyr g Asp r Leu 530 r Asp r Tyr n Glu r Lys r Phe 610 y Val	Leu Gln 435 Tyr Tyr Arg Glu Arg 515 Tyr Thr Ser Arg Arg 595 Asn	Gly 420 Leu Ala Arg Pro 500 Leu Ile Trp Leu Ile 580 Arg Ala	A05 Asn Ala Lys Tyr Met 485 Ile Gln Ser Tyr Ser 565 Val Tyr	Trp Asp Ser 470 Glu Ile Leu Gly Gln 550 Phe Gly Thr	Gly Ala Met 455 Thr Gly Val Asn Thr 535 Val Ser Leu Arg Asn 615	Ala Ser 440 Asn Gln Tyr Asn Val 520 His Gly Trp Asn Glu 600 Ser	Val 425 Arg Thr Gly Glu Tyr 505 Ser Gln Tyr Asn Val 585 Asn	His Phe Phe Tyr 490 His Gln Lys Thr Glu 570 Ser Ala Gly	Leu Glu Gly Tyr 475 Asp Asn Ser Tyr Ser 555 Ser Val Leu Gln	Asp Gly Thr 460 Thr Tyr Leu Leu Trp 540 Ser Val Pro Asp Asn 620	Val Asp 445 Asn Leu Asp Arg Asn 525 Asn Trp Gly Phe Arg 605 Ser	Thr 430 Ser Phe Asp Gly Phe 510 Asp Thr Val Ile Asn 590 Ala Trp	415 His Ile Gln Asp Glu 495 Ser Phe Ser Gly Pro 575 Val Tyr Leu	Ala Arg Leu Val 480 His Arg Gly Asp Ile 560 Asp Leu Ala Ala

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Ser Gln Gly Asp Thr Ser Asn Asn Gly Tyr Thr Gly Ser Ala Thr Ala
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                              650
Asn Trp Gln Ala Ala Tyr Gly Thr Leu Gly Gly Gly Tyr Asn Tyr Asp
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Arg Asp Gln His Asp Val Asn Trp Gln Leu Ser Gly Gly Val Val Gly
              680
His Glu Asn Gly Ile Thr Leu Ser Gln Pro Leu Gly Asp Thr Asn Val
                 695
Leu Ile Lys Ala Pro Gly Ala Gly Gly Val Arg Ile Glu Asn Gln Thr
    710 715
Gly Ile Leu Thr Asp Trp Arg Gly Tyr Ala Val Met Leu Tyr Ala Thr
            725 730 735
Val Tyr Arg Tyr Asn Arg Ile Ala Leu Asp Thr Asn Thr Met Gly Asn
       740 745
Ser Ile Asp Val Glu Lys Asn Ile Ser Ser Val Val Pro Thr Gln Gly
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Ala Leu Val Arg Ala Asn Phe Asp Thr Arg Ile Gly Val Arg Ala Leu
 770 775
                                      780
Ile Thr Val Thr Gln Gly Gly Lys Pro Val Pro Phe Gly Ser Leu Val
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Arg Glu Asn Ser Thr Gly Ile Thr Ser Met Val Gly Asp Asp Gly Gln
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                              810
Val Tyr Leu Ser Gly Ala Pro Leu Ser Gly Glu Leu Leu Val Gln Trp
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Gly Asp Gly Ala Asn Ser Arg Cys Ile Ala His Tyr Val Leu Pro Lys
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Pro Gly Ser
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 35 40
Lys Ser Gly Trp Val Gly Val Ser Ala Ile Cys Pro Pro Gly Thr Leu
Val Asn Tyr Thr Tyr Arg Ser Tyr Val Thr Asn Phe Ile Val Gln Glu
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                                  75
Thr Ile Asp Asn Tyr Lys Tyr Met Gln Leu His Asp Tyr Leu Leu Gly
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                              90
Ala Met Ser Leu Val Asp Ser Val Met Asp Ile Gln Phe Pro Pro Gln
                           105
Asn Tyr Ile Arg Met Gly Thr Asp Pro Asn Val Ser Gln Asn Leu Pro
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Phe Gly Val Met Asp Ser Arg Leu Ile Phe Arg Leu Lys Val Ile Arg
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                                     140
Pro Phe Ile Asn Met Val Glu Ile Pro Arg Gln Val Met Phe Thr Val
     150 155
Tyr Val Thr Ser Thr Pro Tyr Asp Pro Leu Val Thr Pro Val Tyr Thr
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                                                175
Ile Ser Phe Gly Gly Arg Val Glu Val Pro Gln Asn Cys Glu Leu Asn
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185
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Thr Lys Ser Ile Ala Val Lys Cys Thr Asn Val Ala Ala Gln Ala Tyr
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225 230
Leu Thr Met Arg Leu Glu Ala Ser Ala Val Ser Gly Gln Ala Met Val
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Ser Asp Asn Gln Asp Leu Gly Phe Ile Val Ala Asp Gln Asn Asp Thr
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Pro Ile Thr Pro Asn Asp Leu Asn Ser Val Ile Pro Phe Arg Leu Asp
                        280
                                         285
Ala Ala Ala Ala Asn Val Thr Leu Arg Ala Trp Pro Ile Ser Ile
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Arg Val Asp Tyr Gln
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Pro Pro Gly Ser Val Ala Ile Leu Phe Thr Gly Thr Pro Ala Ser Asp
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Thr Asn Leu Leu Ala Leu Asp Asp Pro Ala Met Ala Gln Thr Val Ala
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Ile Glu Leu Arg Asn Ser Asp Arg Ser Arg Leu Ala Leu Gly Glu Ala
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                                         125
Ser Pro Thr Glu Glu Val Asp Ala Asn Gly Asn Val Thr Leu Asn Phe
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Asp Tyr Tyr Ala Glu Asn Arg His Phe Leu Lys Pro Trp Glu Pro Val
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Met Ile Asn Glu Phe His Lys Gln Gly Ser Ala Phe Tyr Phe Gly Leu
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Phe Asp Pro Asp Glu Lys Glu Ile Ile Gly Val Ala Asn Phe Ser Asn
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Val Val Arg Gly Ser Phe His Ala Cys Tyr Leu Gly Tyr Ser Ile Gly
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          100
Gln Lys Trp Gln Gly Lys Gly Leu Met Phe Glu Ala Leu Thr Ala Ala
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Ile Arg Tyr Met Gln Arg Thr Gln His Ile His Arg Ile Met Ala Asn
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                               140
Tyr Met Pro His Asn Lys Arg Ser Gly Asp Leu Leu Ala Arg Leu Gly
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        150
Phe Glu Lys Glu Gly Tyr Ala Lys Asp Tyr Leu Leu Ile Asp Gly Gln
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Asn Leu Ser Glu Ser Glu Val Gln Glu Gln Leu Asp Asn Leu Val Lys
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Tyr Glu Gln Arg Phe Cys Asn Ser Glu Phe Gly Asp Leu Lys Leu Ser
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                                               110
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                                            125
Asp Met Ala Glu Val Glu Ser Thr Leu Glu Gln Leu Ala Asn Arg Glu
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                                         140
Asp Gly Pro Phe Val Val Arg Leu Ala Arg Glu Pro Gly Lys Arg Glu
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Asn Arg Tyr Met His Leu Phe Ser Gly Glu Val Glu Asp Gln Pro Ala
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Val Thr Asp Met Ser Asn Ala Val Asp Gly Asp Leu Gln Ala Arg Val
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Leu Leu Ala His Leu Gly Asp
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-334-

<213> Escherichia coli

<400> 362

Met Lys Lys Leu Arg Ile Gly Val Val Gly Leu Gly Gly Ile Ala Gln 10 Lys Ala Trp Leu Pro Val Leu Ala Ala Ala Ser Asp Trp Thr Leu Gln 20 25 Gly Ala Trp Ser Pro Thr Arg Ala Lys Ala Leu Pro Ile Cys Glu Ser 40 Trp Arg Ile Pro Tyr Ala Asp Ser Leu Ser Ser Leu Ala Ala Ser Cys 55 60 Asp Ala Val Phe Val His Ser Ser Thr Ala Ser His Phe Asp Val Val 70 75 Ser Thr Leu Leu Asn Ala Gly Val His Val Cys Val Asp Lys Pro Leu 90 85 Ala Glu Asn Leu Arg Asp Ala Glu Arg Leu Val Glu Leu Ala Ala Arg 105 Lys Lys Leu Thr Leu Met Val Gly Phe Asn Arg Arg Phe Ala Pro Leu 120 125 Tyr Gly Glu Leu Lys Thr Gln Leu Ala Thr Ala Ala Ser Leu Arg Met 135 140 Asp Lys His Arg Ser Asn Ser Val Gly Pro His Asp Leu Tyr Phe Thr 150 155 Leu Leu Asp Asp Tyr Leu His Val Val Asp Thr Ala Leu Trp Leu Ser 170 165 Gly Gly Lys Ala Ser Leu Asp Gly Gly Thr Leu Leu Thr Asn Asp Ala 180 185 Gly Glu Met Leu Phe Ala Glu His His Phe Ser Ala Gly Pro Leu Gln 200 Ile Thr Thr Cys Met His Arg Arg Ala Gly Ser Gln Arg Glu Thr Val 215 Gln Ala Val Thr Asp Gly Ala Leu Ile Asp Ile Thr Asp Met Arg Glu 230 235 Trp Arg Glu Glu Arg Gly Gln Gly Val Val His Lys Pro Ile Pro Gly 245 250 Trp Gln Ser Thr Leu Glu Gln Arg Gly Phe Val Gly Cys Ala Arg His 265 Phe Ile Glu Cys Val Gln Asn Gln Thr Val Pro Gln Thr Ala Gly Glu Gin Ala Val Leu Ala Gin Arg Ile Val Asp Lys Ile Trp Arg Asp Ala 295 300 Met Ser Glu 305 <210> 363 <211> 239 <212> PRT <213> Escherichia coli <400> 363 Met Leu Lys Arg Val Phe Leu Ser Leu Leu Val Leu Ile Gly Leu Leu 10 Leu Leu Thr Val Leu Gly Leu Asp Arg Trp Met Ser Trp Lys Thr Ala 20 25 Pro Tyr Ile Tyr Asp Glu Leu Gln Asp Leu Pro Tyr Arg Gln Val Gly Val Val Leu Gly Thr Ala Lys Tyr Tyr Arg Thr Gly Val Ile Asn Gln Tyr Tyr Arg Tyr Arg Ile Gln Gly Ala Ile Asn Ala Tyr Asn Ser Gly 75

```
Lys Val Asn Tyr Leu Leu Leu Ser Gly Asp Asn Ala Leu Gln Ser Tyr
                                   90
                85
Asn Glu Pro Met Thr Met Arg Lys Asp Leu Ile Ala Ala Gly Val Asp
            100
                               105
Pro Ser Asp Ile Val Leu Asp Tyr Ala Gly Phe Arg Thr Leu Asp Ser
                           120
Ile Val Arg Thr Arg Lys Val Phe Asp Thr Asn Asp Phe Ile Ile Ile
                      135
Thr Gln Arg Phe His Cys Glu Arg Ala Leu Phe Ile Ala Leu His Met
               150
                                155
Gly Ile Gln Ala Gln Cys Tyr Ala Val Pro Ser Pro Lys Asp Met Leu
                                  170
               165
Ser Val Arg Ile Arg Glu Phe Ala Ala Arg Phe Gly Ala Leu Ala Asp
                               185
Leu Tyr Ile Phe Lys Arg Glu Pro Arg Phe Leu Gly Pro Leu Val Pro
                           200
Ile Pro Ala Met His Gln Val Pro Glu Asp Ala Gln Gly Tyr Pro Ala
                       215
                                          220
Val Thr Pro Glu Gln Leu Leu Glu Leu Gln Lys Lys Gln Gly Lys
<210> 364
<211> 79
<212> PRT
<213> Escherichia coli
<400> 364
Met Asp Val Gln Gln Phe Phe Val Val Ala Val Phe Phe Leu Ile Pro
Ile Phe Cys Phe Arg Glu Ala Trp Lys Gly Trp Arg Ala Gly Ala Ile
                                25
Asp Lys Arg Val Lys Asn Ala Pro Glu Pro Val Tyr Val Trp Arg Ala
                           40
Lys Asn Pro Gly Leu Phe Phe Ala Tyr Met Val Ala Tyr Ile Gly Phe
                       55
Gly Ile Leu Ser Ile Gly Met Ile Val Tyr Leu Ile Phe Tyr Arg
                    70
<210> 365
<211> 510
<212> PRT
<213> Escherichia coli
<400> 365
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Gly Pro Asp Trp Thr Phe Asp Leu Leu Asp Val Tyr Leu Ala Glu Ile
                                25
Asp Arg Val Ala Lys Leu Tyr Arg Leu Asp Thr Tyr Pro His Gln Ile
                           40
Glu Val Ile Thr Ser Glu Gln Met Met Asp Ala Tyr Ser Ser Val Gly
                       55
                                           60
Met Pro Ile Asn Tyr Pro His Trp Ser Phe Gly Lys Lys Phe Ile Glu
                    70
                                       75
Thr Glu Arg Leu Tyr Lys His Gly Gln Gln Gly Leu Ala Tyr Glu Ile
              85
Val Ile Asn Ser Asn Pro Cys Ile Ala Tyr Leu Met Glu Glu Asn Thr
           100
                                105
Ile Thr Met Gln Ala Leu Val Met Ala His Ala Cys Tyr Gly His Asn
                           120
                                               125
```

```
Ser Phe Phe Lys Asn Asn Tyr Leu Phe Arg Ser Trp Thr Asp Ala Ser
           135
                              140
Ser Ile Val Asp Tyr Leu Ile Phe Ala Arg Lys Tyr Ile Thr Glu Cys
                                      155
                  150
Glu Glu Arg Tyr Gly Val Asp Glu Val Glu Arg Leu Leu Asp Ser Cys
                                  170
               165
His Ala Leu Met Asn Tyr Gly Val Asp Arg Tyr Lys Arg Pro Gln Lys
                              185
Ile Ser Leu Gln Glu Glu Lys Ala Arg Gln Lys Ser Arg Glu Glu Tyr
                          200
Leu Gln Ser Gln Val Asn Met Leu Trp Arg Thr Leu Pro Lys Arg Glu
                      215
                                         220
Glu Glu Lys Thr Val Ala Glu Ala Arg Arg Tyr Pro Ser Glu Pro Gln
                  230
                                     235
Glu Asn Leu Leu Tyr Phe Met Glu Lys Asn Ala Pro Leu Leu Glu Ser
                                  250
Trp Gln Arg Glu Ile Leu Arg Ile Val Arg Lys Val Ser Gln Tyr Phe
                              265
           260
Tyr Pro Gln Lys Gln Thr Gln Val Met Asn Glu Gly Trp Ala Thr Phe
                       280
Trp His Tyr Thr Ile Leu Asn His Leu Tyr Asp Glu Gly Lys Val Thr
                      295
Glu Arq Phe Met Leu Glu Phe Leu His Ser His Thr Asn Val Val Phe
                   310
                                     315
Gln Pro Pro Tyr Asn Ser Pro Trp Tyr Ser Gly Ile Asn Pro Tyr Ala
              325
                                 330
Leu Gly Phe Ala Met Phe Gln Asp Ile Lys Arg Ile Cys Gln Ser Pro
                              345
          340
Thr Glu Glu Asp Lys Tyr Trp Phe Pro Asp Ile Ala Gly Ser Asp Trp
                          360
Leu Glu Thr Leu His Phe Ala Met Arg Asp Phe Lys Asp Glu Ser Phe
                     375
                                      380
Ile Ser Gln Phe Leu Ser Pro Lys Val Met Arg Asp Phe Arg Phe Phe
                                   395
                  390
Thr Val Leu Asp Asp Asp Arg His Asn Tyr Leu Glu Ile Ser Ala Ile
                                  410
His Asn Glu Glu Gly Tyr Arg Glu Ile Arg Asn Arg Leu Ser Ser Gln
                               425
Tyr Asn Leu Ser Asn Leu Glu Pro Asn Ile Gln Ile Trp Asn Val Asp
                          440
                                              445
Leu Arg Gly Asp Arg Ser Leu Thr Leu Arg Tyr Ile Pro His Asn Arg
                      455
                                         460
Ala Pro Leu Asp Arg Gly Arg Lys Glu Val Leu Lys His Val His Arg
                   470
                                     475
Leu Trp Gly Phe Asp Val Met Leu Glu Gln Gln Asn Glu Asp Gly Ser
              485
                                 490
Ile Glu Leu Leu Glu Arg Cys Pro Pro Arg Met Gly Asn Leu
                              505
<210> 366
<211> 452
<212> PRT
<213> Escherichia coli
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<400> 366

 Met
 Lys
 Arg
 Leu
 Ser
 Ile
 Thr
 Val
 Arg
 Leu
 Thr
 Leu
 Phe
 Ile
 Leu

 1
 5
 10
 10
 15

 Leu
 Leu
 Ser
 Val
 Ala
 Gly
 Ala
 Gly
 Ile
 Val
 Trp
 Thr
 Leu
 Tyr
 Asn
 Gly

 Leu
 Ala
 Ser
 Glu
 Leu
 Lys
 Trp
 Arg
 Asp
 Asp
 Thr
 Thr
 Leu
 Ile
 Asn
 Arg

```
Thr Ala Gln Ile Lys Gln Leu Leu Ile Asp Gly Val Asn Pro Asp Thr
Leu Pro Val Tyr Phe Asn Arg Met Met Asp Val Ser Gln Asp Ile Leu
                   70
Ile Ile His Gly Asp Ser Ile Asn Lys Ile Val Asn Arg Thr Asn Val
                                 90
              85
Ser Asp Gly Met Leu Asn Asn Ile Pro Ala Ser Glu Thr Ile Ser Ala
                             105
Ala Gly Ile Tyr Arg Ser Ile Ile Asn Asp Thr Glu Ile Asp Ala Leu
                         120
                                            125
Arg Ile Asn Ile Asp Glu Val Ser Pro Ser Leu Thr Val Thr Val Ala
            135
                               140
Lys Leu Ala Ser Ala Arg His Asn Met Leu Glu Gln Tyr Lys Ile Asn
                150
                                     155
Ser Ile Ile Cys Ile Val Ala Ile Val Leu Cys Ser Val Leu Ser
                                  170
               165
Pro Leu Leu Ile Arg Thr Gly Leu Arg Glu Ile Lys Lys Leu Ser Gly
                             185
           180
Val Thr Glu Ala Leu Asn Tyr Asn Asp Ser Arg Glu Pro Val Glu Val
                         200
Ser Ala Leu Pro Arg Glu Leu Lys Pro Leu Gly Gln Ala Leu Asn Lys
                      215
                                        220
Met His His Ala Leu Val Lys Asp Phe Glu Arg Leu Ser Gln Phe Ala
                  230
                          235
Asp Asp Leu Ala His Glu Leu Arg Thr Pro Ile Asn Ala Leu Leu Gly
                                 250
              245
Gln Asn Gln Val Thr Leu Ser Gln Thr Arg Ser Ile Ala Glu Tyr Gln
           260
                              265
Lys Thr Ile Ala Gly Asn Ile Glu Glu Leu Glu Asn Ile Ser Arg Leu
                          280
Thr Glu Asn Ile Leu Phe Leu Ala Arg Ala Asp Lys Asn Asn Val Leu
                     295
                                         300
Val Lys Leu Asp Ser Leu Ser Leu Asn Lys Glu Val Glu Asn Leu Leu
                                     315
               310
Asp Tyr Leu Glu Tyr Leu Ser Asp Glu Lys Glu Ile Cys Phe Lys Val
                     330
              325
Glu Cys Asn Gln Gln Ile Phe Ala Asp Lys Ile Leu Leu Gln Arg Met
                             345
Leu Ser Asn Leu Ile Val Asn Ala Ile Arg Tyr Ser Pro Glu Lys Ser
                         360
Arg Ile His Ile Thr Ser Phe Leu Asp Thr Asn Ser Tyr Leu Asn Ile
                       375
Asp Ile Ala Ser Pro Gly Thr Lys Ile Asn Glu Pro Glu Lys Leu Phe
                   390
                                      395
Arg Arg Phe Trp Arg Gly Asp Asn Ser Arg His Ser Val Gly Gln Gly
               405
                                  410
Leu Gly Leu Ser Leu Val Lys Ala Ile Ala Glu Leu His Gly Gly Ser
                              425
Ala Thr Tyr His Tyr Leu Asn Lys His Asn Val Phe Arg Ile Thr Leu
       435
Pro Gln Arg Asn
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<210> 367
<211> 239
<212> PRT
<213> Escherichia coli
<400> 367
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Met Asn Gln Ala Val Ser Ile Thr Tyr Asp Leu Trp His Ile Ile Phe
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Met Lys Ile Leu Leu Ile Glu Asp Asn Gln Arg Thr Gln Glu Trp Val
                              25
Thr Gln Gly Leu Ser Glu Ala Gly Tyr Val Ile Asp Ala Val Ser Asp
Gly Arg Asp Gly Leu Tyr Leu Ala Leu Lys Asp Asp Tyr Ala Leu Ile
Ile Leu Asp Ile Met Leu Pro Gly Met Asp Gly Trp Gln Ile Leu Gln
                                      75
                   70
Thr Leu Arg Thr Ala Lys Gln Thr Pro Val Ile Cys Leu Thr Ala Arg
                                  90
Asp Ser Val Asp Asp Arg Val Arg Gly Leu Asp Ser Gly Ala Asn Asp
                              105
           100
Tyr Leu Val Lys Pro Phe Ser Phe Ser Glu Leu Leu Ala Arg Val Arg
                                             125
                          120
Ala Gln Leu Arg Gln His His Ala Leu Asn Ser Thr Leu Glu Ile Ser
                      135 . 140
Gly Leu Arg Met Asp Ser Val Ser His Ser Val Ser Arg Asp Asn Ile
                  150
                                      155
Ser Ile Thr Leu Thr Arg Lys Glu Phe Gln Leu Leu Trp Leu Leu Ala
                                  170
               165
Ser Arg Ala Gly Glu Ile Ile Pro Arg Thr Val Ile Ala Ser Glu Ile
                             185
           180
Trp Gly Ile Asn Phe Asp Ser Asp Thr Asn Thr Val Asp Val Ala Ile
                 200
Arg Arg Leu Arg Ala Lys Val Asp Asp Pro Phe Pro Glu Lys Leu Ile
                                          220
                      215
Ala Thr Ile Arg Gly Met Gly Tyr Ser Phe Val Ala Val Lys Lys
<210> 368
<211> 172
<212> PRT
<213> Escherichia coli
<400> 368
Met Ile Leu Lys Ser Ala Ile Ser Ala Asp Ser Leu Leu Ala Lys Asp
                                  10 15
Ala Phe Arg Ala Ser Phe His Leu His Phe Leu Arg Asn His Gly Ile
                               25
Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg Tyr
                           40
        35
Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile Lys
                                           60
Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala Trp
                   70
                                      75
Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser Lys
                                   90
               85
Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro Gly
                               105
           100
Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys Gln
                           120
Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp Thr
                       135
                                          140
Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys Ile
                                      155
                   150
Ile Lys Ala Tyr Asp Gly Glu Ile Phe Tyr His Arg
```

165

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<211> 274
<212> PRT
<213> Escherichia coli
<400> 369
Met Thr Glu Phe Thr Thr Leu Leu Gln Gln Gly Asn Ala Trp Phe Phe
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Ile Pro Ser Ala Ile Leu Leu Gly Ala Leu His Gly Leu Glu Pro Gly
His Ser Lys Thr Met Met Ala Ala Phe Ile Ile Ala Ile Lys Gly Thr
                           40
Ile Lys Gln Ala Val Met Leu Gly Leu Ala Ala Thr Ile Ser His Thr
                   55
Ala Val Val Trp Leu Ile Ala Phe Gly Gly Met Val Ile Ser Lys Arg
Phe Thr Ala Gln Ser Ala Glu Pro Trp Leu Gln Leu Ile Ser Ala Val
               85
                                   90
Ile Ile Ile Ser Thr Ala Phe Trp Met Phe Trp Arg Thr Trp Arg Gly
           100
                              105
                                                   110
Glu Arg Asn Trp Leu Glu Asn Met His Gly His Asp Tyr Glu His His
                           120
His His Asp His Glu His His His Asp His Gly His His His His
                       135
Glu His Gly Glu Tyr Gln Asp Ala His Ala Arg Ala His Ala Asn Asp
                   150
                                      155
Ile Lys Arg Arg Phe Asp Gly Arg Glu Val Thr Asn Trp Gln Ile Leu
              165
                                  170
Leu Phe Gly Leu Thr Gly Gly Leu Ile Pro Cys Pro Ala Ala Ile Thr
                               185
                                                  190
           180
Val Leu Leu Ile Cys Ile Gln Leu Lys Ala Leu Thr Leu Gly Ala Thr
                           200
Leu Val Val Ser Phe Ser Ile Gly Leu Ala Leu Thr Leu Val Thr Val
                       215
                                          220
Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser
                  230
                                      235
Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu
                                  250
Ile Gly Leu Val Gly Val Tyr Met Gly Val His Gly Phe Met Gly Ile
                               265
Met Arg
<210> 370
<211> 82
<212> PRT
<213> Escherichia coli
<400> 370
Met Cys Ile Gly Val Pro Gly Gln Val Leu Ala Val Gly Glu Asp Ile
His Gln Leu Ala Gln Val Glu Val Cys Gly Ile Lys Arg Asp Val Asn
                               25
Ile Ala Leu Ile Cys Glu Gly Asn Pro Ala Asp Leu Leu Gly Gln Trp
                           40
Val Leu Val His Val Gly Phe Ala Met Ser Ile Ile Asp Glu Asp Glu
                       55
                                           60
Ala Lys Ala Thr Leu Asp Ala Leu Arg Gln Met Asp Tyr Asp Ile Thr
65
Ser Ala
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<210> 371
<211> 113
<212> PRT
<213> Escherichia coli
<400> 371
Met His Glu Leu Ser Leu Cys Gln Ser Ala Val Glu Ile Ile Gln Arg
1 5
                             10
Gln Ala Glu Gln His Asp Val Lys Arg Val Thr Ala Val Trp Leu Glu
                                         30
                         25
Ile Gly Ala Leu Ser Cys Val Glu Glu Ser Ala Val Arg Phe Ser Phe
                              45
                    40
Glu Ile Val Cys His Gly Thr Val Ala Gln Gly Cys Asp Leu His Ile
 50 55
Val Tyr Lys Pro Ala Gln Ala Trp Cys Trp Asp Cys Ser Gln Val Val
              70
                               75
Glu Ile His Gln His Asp Ala Gln Cys Pro Leu Cys His Gly Glu Arg
            85
                    90
Leu Arg Val Asp Thr Gly Asp Ser Leu Ile Val Lys Ser Ile Glu Val
          100 105
Glu
<210> 372
<211> 162
<212> PRT
<213> Escherichia coli
<400> 372
Met Thr Glu Glu Ile Ala Gly Phe Gln Thr Ser Pro Lys Ala Gln Val
                       10 15
Gln Ala Ala Phe Glu Glu Ile Ala Arg Arg Ser Met His Asp Leu Ser
Phe Leu His Pro Ser Met Pro Val Tyr Val Ser Asp Phe Thr Leu Phe
                              45
 35 40
Glu Gly Gln Trp Thr Gly Cys Val Ile Thr Pro Trp Met Leu Ser Ala
            55
Val Ile Phe Pro Gly Pro Asp Gln Leu Trp Pro Leu Arg Lys Val Ser
                       75 80
                70
Glu Lys Ile Gly Leu Gln Leu Pro Tyr Gly Thr Met Thr Phe Thr Val
                          90
Gly Glu Leu Asp Gly Val Ser Gln Tyr Leu Ser Cys Ser Leu Met Ser
                       105 110
          100
Pro Leu Ser His Ser Met Ser Ile Glu Glu Gly Gln Arg Leu Thr Asp
 115 120
Asp Cys Ala Arg Met Ile Leu Ser Leu Pro Val Thr Asn Pro Asp Val
 130 135
                         140
Pro His Ala Gly Arg Arg Ala Leu Leu Phe Gly Arg Arg Ser Gly Glu
                150
Asn Ala
<210> 373
<211> 164
<212> PRT
<213> Escherichia coli
<400> 373
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Met Arg Ile Leu Val Leu Gly Val Gly Asn Ile Leu Leu Thr Asp Glu Ala Ile Gly Val Arg Ile Val Glu Ala Leu Glu Gln Arg Tyr Ile Leu Pro Asp Tyr Val Glu Ile Leu Asp Gly Gly Thr Ala Gly Met Glu Leu Leu Gly Asp Met Ala Asn Arg Asp His Leu Ile Ile Ala Asp Ala Ile Val Ser Lys Lys Asn Ala Pro Gly Thr Met Met Ile Leu Arg Asp Glu 70 75 Glu Val Pro Ala Leu Phe Thr Asn Lys Ile Ser Pro His Gln Leu Gly 85 90 Leu Ala Asp Val Leu Ser Ala Leu Arg Phe Thr Gly Glu Phe Pro Lys 105 Lys Leu Thr Leu Val Gly Val Ile Pro Glu Ser Leu Glu Pro His Ile 120 Gly Leu Thr Pro Thr Val Glu Ala Met Ile Glu Pro Ala Leu Glu Gln 135 140 Val Leu Ala Ala Leu Arg Glu Ser Gly Val Glu Ala Ile Pro Arg Glu 150 Ala Ile His Asp

<210> 374

<211> 567

<212> PRT

<213> Escherichia coli

<400> 374

Met Ser Gln Arg Ile Thr Ile Asp Pro Val Thr Arg Ile Glu Gly His 10 Leu Arg Ile Asp Cys Glu Ile Glu Asn Gly Val Val Ser Lys Ala Trp 20 25 Ala Ser Gly Thr Met Trp Arg Gly Met Glu Glu Ile Val Lys Asn Arg Asp Pro Arg Asp Ala Trp Met Ile Val Gln Arg Ile Cys Gly Val Cys Thr Thr His Ala Leu Ser Ser Val Arg Ala Ala Glu Ser Ala Leu 70 75 Asn Ile Asp Val Pro Val Asn Ala Gln Tyr Ile Arg Asn Ile Ile Leu 90 85 Ala Ala His Thr Thr His Asp His Ile Val His Phe Tyr Gln Leu Ser 105 Ala Leu Asp Trp Val Asp Ile Thr Ser Ala Leu Gln Ala Asp Pro Thr 120 Lys Ala Ser Glu Met Leu Lys Gly Val Ser Thr Trp His Leu Asn Ser 135 140 Pro Glu Glu Phe Thr Lys Val Gln Asn Lys Ile Lys Asp Leu Val Ala 155 150 Ser Gly Gln Leu Gly Ile Phe Ala Asn Gly Tyr Trp Gly His Pro Ala 170 Met Lys Leu Pro Pro Glu Val Asn Leu Ile Ala Val Ala His Tyr Leu 185 Gln Ala Leu Glu Cys Gln Arg Asp Ala Asn Arg Val Val Ala Leu Leu 200 205 Gly Gly Lys Thr Pro His Ile Gln Asn Leu Ala Val Gly Gly Val Ala 215 220 Asn Pro Ile Asn Leu Asp Gly Leu Gly Val Leu Asn Leu Glu Arg Leu 235 230 Met Tyr Ile Lys Ser Phe Ile Asp Lys Leu Ser Asp Phe Val Glu Gln

250

Val Tyr Lys Val Asp Thr Ala Val Ile Ala Ala Phe Tyr Pro Glu Trp

245 .

```
265
         260
Leu Thr Arg Gly Lys Gly Ala Val Asn Tyr Leu Ser Val Pro Glu Phe
                       280
Pro Thr Asp Ser Lys Asn Gly Ser Phe Leu Phe Pro Gly Gly Tyr Ile
                            300
         295
Glu Asn Ala Asp Leu Ser Ser Tyr Arg Pro Ile Thr Ser His Ser Asp
                        315
       310
Glu Tyr Leu Ile Lys Gly Ile Gln Glu Ser Ala Lys His Ser Trp Tyr
                     330
      325
Lys Asp Glu Ala Pro Gln Ala Pro Trp Glu Gly Thr Thr Ile Pro Ala
                          345 350
Tyr Asp Gly Trp Ser Asp Asp Gly Lys Tyr Ser Trp Val Lys Ser Pro
                      360 365
Thr Phe Tyr Gly Lys Thr Val Glu Val Gly Pro Leu Ala Asn Met Leu
                    375
                                     380
Val Lys Leu Ala Ala Gly Arg Glu Ser Thr Gln Asn Lys Leu Asn Glu
                390
                                 395
Ile Val Ala Ile Tyr Gln Lys Leu Thr Gly Asn Thr Leu Glu Val Ala
                              410
Gln Leu His Ser Thr Leu Gly Arg Ile Ile Gly Arg Thr Val His Cys
                           425
                                         430
Cys Glu Leu Gln Asp Ile Leu Gln Asn Gln Tyr Ser Ala Leu Ile Thr
                       440
                                        445
Asn Ile Gly Lys Gly Asp His Thr Thr Phe Val Lys Pro Asn Ile Pro
                    455
Ala Thr Gly Glu Phe Lys Gly Val Gly Phe Leu Glu Ala Pro Arg Gly
                470
                               475
Met Leu Ser His Trp Met Val Ile Lys Asp Gly Ile Ile Ser Asn Tyr
                    490
            485
Gln Ala Val Val Pro Ser Thr Trp Asn Ser Gly Pro Arg Asn Phe Asn
                          505
         500
Asp Asp Val Gly Pro Tyr Glu Gln Ser Leu Val Gly Thr Pro Val Ala
                       520
Asp Pro Asn Lys Pro Leu Glu Val Val Arg Thr Ile His Ser Phe Asp
 530 , 535
                           540
Pro Cys Met Ala Cys Ala Val His Val Val Asp Ala Asp Gly Asn Glu
      550 555
Val Val Ser Val Lys Val Leu .
             565
<210> 375
<211> 392
<212> PRT
<213> Escherichia coli
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1
             5
Val Met Ile Phe Gly Pro Leu Ile Val Ile Cys Met Leu Leu Ile Val
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Lys Arg Leu Val Phe Gly Leu Gly Ser Val Ser Asp Leu Asn Gly Gly
             40
                                        45
Phe Pro Trp Gly Val Trp Ile Ala Phe Asp Leu Leu Ile Gly Thr Gly
                    55
                                     60
Phe Ala Cys Gly Gly Trp Ala Leu Ala Trp Ala Val Tyr Val Phe Asn
                 70
Arg Gly Gln Tyr His Pro Leu Val Arg Pro Ala Leu Leu Ala Ser Leu
                               90
```

Phe Gly Tyr Ser Leu Gly Gly Leu Ser Ile Thr Ile Asp Val Gly Arg

```
105
Tyr Trp Asn Leu Pro Tyr Phe Tyr Ile Pro Gly His Phe Asn Val Asn
                          120
Ser Val Leu Phe Glu Thr Ala Val Cys Met Thr Ile Tyr Ile Gly Val
                      135
Met Ala Leu Glu Phe Ala Pro Ala Leu Phe Glu Arg Leu Gly Trp Lys
                150 155
Val Ser Leu Gln Arg Leu Asn Lys Val Met Phe Phe Ile Ile Ala Leu
                                170
            165
Gly Ala Leu Leu Pro Thr Met His Gln Ser Ser Met Gly Ser Leu Met
          180 185
Ile Ser Ala Gly Tyr Lys Val His Pro Leu Trp Gln Ser Tyr Glu Met
                  200
Leu Pro Leu Phe Ser Leu Leu Thr Ala Phe Ile Met Gly Phe Ser Ile
          215
Val Ile Phe Glu Gly Ser Leu Val Gln Ala Gly Leu Arg Gly Asn Gly
                                     235
                   230
Pro Asp Glu Lys Ser Leu Phe Val Lys Leu Thr Asn Thr Ile Ser Val
                                 250
Leu Leu Ala Ile Phe Ile Val Leu Arg Phe Gly Glu Leu Ile Tyr Arg
                             265
           260
Asp Lys Leu Ser Leu Ala Phe Ala Gly Asp Phe Tyr Ser Val Met Phe
                         280
Trp Ile Glu Val Leu Leu Met Leu Phe Pro Leu Val Val Leu Arg Val
                                        300
                     295
Ala Lys Leu Arg Asn Asp Ser Arg Met Leu Phe Leu Ser Ala Leu Ser
                              315
                  310
Ala Leu Leu Gly Cys Ala Thr Trp Arg Leu Thr Tyr Ser Leu Val Ala
                                  330
               325
Phe Asn Pro Gly Gly Gly Tyr Ala Tyr Phe Pro Thr Trp Glu Glu Leu
                              345
           340
Leu Ile Ser Ile Gly Phe Val Ala Ile Glu Ile Cys Ala Tyr Ile Val
                       360
                                            365
Leu Ile Arg Leu Leu Pro Ile Leu Pro Pro Leu Lys Gln Asn Asp His
            375
Asn Arg His Glu Ala Ser Lys Ala
<210> 376
<211> 328
<212> PRT
<213> Escherichia coli
<400> 376
Met Asn Arg Arg Asn Phe Ile Lys Ala Ala Ser Cys Gly Ala Leu Leu
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                                                 . 15
Thr Gly Ala Leu Pro Ser Val Ser His Ala Ala Ala Glu Asn Arg Pro
                              25
Pro Ile Pro Gly Ser Leu Gly Met Leu Tyr Asp Ser Thr Leu Cys Val
                          40
Gly Cys Gln Ala Cys Val Thr Lys Cys Gln Asp Ile Asn Phe Pro Glu
Arg Asn Pro Gln Gly Glu Gln Thr Trp Ser Asn Asn Asp Lys Leu Ser
                                     75
Pro Tyr Thr Asn Asn Ile Ile Gln Val Trp Thr Ser Gly Thr Gly Val
                                  90
Asn Lys Asp Gln Glu Glu Asn Gly Tyr Ala Tyr Ile Lys Lys Gln Cys
                              105
                                                110
Met His Cys Val Asp Pro Asn Cys Val Ser Val Cys Pro Val Ser Ala
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120
Leu Lys Lys Asp Pro Lys Thr Gly Ile Val His Tyr Asp Lys Asp Val
                                 140
                   135
Cys Thr Gly Cys Arg Tyr Cys Met Val Ala Cys Pro Tyr Asn Val Pro
                                 155
                150
Lys Tyr Asp Tyr Asn Asn Pro Phe Gly Ala Leu His Lys Cys Glu Leu
                    170
Cys Asn Gln Lys Gly Val Glu Arg Leu Asp Lys Gly Gly Leu Pro Gly
                 185
Cys Val Glu Val Cys Pro Ala Gly Ala Val Ile Phe Gly Thr Arg Glu
                        200
Glu Leu Met Ala Glu Ala Lys Lys Arg Leu Ala Leu Lys Pro Gly Ser
                                      220
                    215
Glu Tyr His Tyr Pro Arg Gln Thr Leu Lys Ser Gly Asp Thr Tyr Leu
                230
                                 235
His Thr Val Pro Lys Tyr Tyr Pro His Leu Tyr Gly Glu Lys Glu Gly
              245
                              250
Gly Gly Thr Gln Val Leu Val Leu Thr Gly Val Pro Tyr Glu Asn Leu
                          265
Asp Leu Pro Lys Leu Asp Asp Leu Ser Thr Gly Ala Arg Ser Glu Asn
                                285
                      280
Ile Gln His Thr Leu Tyr Lys Gly Met Met Leu Pro Leu Ala Val Leu
                    295
                         300
Ala Gly Leu Thr Val Leu Val Arg Arg Asn Thr Lys Asn Asp His His
       310
Asp Gly Gly Asp Asp His Glu Ser
              325
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Met Leu Gln Cys Gly Ala Lys Asn Val Asn Pro Leu Glu Arg Phe Val
                              10
Ser Ser Leu Pro Val Ala Ala Val Leu Pro Glu Leu Leu Thr Ala Leu
                        25
Asp Cys Ala Pro Gln Val Leu Leu Ser Ala Pro Thr Gly Ala Gly Lys
              40
Ser Thr Trp Leu Pro Leu Gln Leu Leu Ala His Pro Gly Ile Asn Gly
                     55
Lys Ile Ile Leu Leu Glu Pro Arg Arg Leu Ala Ala Arg Asn Val Ala
                 70
                                  75
Gln Arg Leu Ala Glu Leu Leu Asn Glu Lys Pro Gly Asp Thr Val Gly
             85
                               90
Tyr Arg Met Arg Ala Gln Asn Cys Val Gly Pro Asn Thr Arg Leu Glu
          100 105
Val Val Thr Glu Gly Val Leu Thr Arg Met Ile Gln Arg Asp Pro Glu
       115 120 125
Leu Ser Gly Val Gly Leu Val Ile Leu Asp Glu Phe His Glu Arg Ser
                    135
                                     140
Leu Gln Ala Asp Leu Ala Leu Ala Leu Leu Leu Asp Val Gln Gln Gly
                150 · 155
Leu Arg Asp Asp Leu Lys Leu Leu Ile Met Ser Ala Thr Leu Asp Asn
             165 170
                                                175
Asp Arg Leu Gln Gln Met Leu Pro Glu Ala Pro Val Val Ile Ser Glu
         180
                           185 190
Gly Arg Ser Phe Pro Val Glu Arg Arg Tyr Leu Pro Leu Pro Ala His
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205

200

C1-	D	Dha	7	n	71-	11-1	7.1.	17-1	n1-	mb	71.	C1	Mat	1 011	70
	210		Asp			215					220				
Gln 225	Glu	Ser	Gly	Ser	Leu 230	Leu	Leu	Phe	Leu	Pro 235	Gly	Val	Gly	Glu	11e 240
Gln	Arg	Val	Gln	Glu 245	Gln	Leu	Ala	Ser	Arg 250	Ile	Gly	Ser	Asp	Val 255	Leu
Leu	Суз	Pro	Leu 260	Tyr	Gly	Ala	Leu	Ser 265	Leu	Asn	Asp	Gln	Arg 270	Lys	Ala
Ile	Leu	Pro 275	Ala	Pro	Gln	Gly	Met 280	Arg	Lys	Val	Val	Leu 285	Ala	Thr	Asn
	290		Thr			295					300				
305			Glu	-	310					315					320
_			Thr	325					330					335	
_	_		Gly 340					345					350		
_		355	Ala				360					365			
	370	_	Leu			375					380				
Ser 385	Asp	Pro	Ala	Gln	Met 390	Ser	Trp	Leu	Asp	Gln 395	Pro	Pro	Val	Val	Asn 400
Leu	Leu	Ala	Ala	Lys 405	Arg	Leu	Leu	Gln	Met 410	Leu	Gly	Ala	Leu	Glu 415	Gly
	_		Ser 420			_		425					430		-
	_	435	Ala				440					445			
	450		Ala	_		455					460				
Gly 465	Asn	Ser	Asp	Leu	Gly 470	Val	Ala	Phe	Ser	Arg 475	Asn	Gln	Pro	Ala	Trp 480
		_	Ser	485					490					495	
		-	Ser 500					505					510		
_	_	515	Ala				520					525			
Asn	Gly 530	Met	Gly	Ala	Met	Leu 535	Asp	Ala	Asn	Asp	Ala 540	Leu	Ser	Arg	His
545	_		Ile		550					555					560
				565					570					575	Gln
_	_		580					585					590		Asp
		595					600					605			Leu
	610	_				615					620				His
Gln 625	Ala	Met	Leu	Asn	Gly 630	Ile	Arg	Asp	Lys	Gly 635	Leu	Ser	Val	Leu	Asn 640
Trp	Thr	Ala	Glu	Ala 645	Glu	Gln	Leu	Arg	Leu 650	Arg	Leu	Leu	Cys	Ala 655	Ala
Lys	Trp	Leu	Pro 660		Tyr	Asp	Trp	Pro 665		Val	Asp	Asp	Glu 670	Ser	Leu
Leu	Ala	Ala 675	Leu	Glu	Thr	Trp	Leu 680	Leu	Pro	His	Met	Thr 685	Gly	Val	His

```
Ser Leu Arg Gly Leu Lys Ser Leu Asp Ile Tyr Gln Ala Leu Arg Gly
                    695
Leu Leu Asp Trp Gly Met Gln Gln Arg Leu Asp Ser Glu Leu Pro Ala
                              715
                 710
His Tyr Thr Val Pro Thr Gly Ser Arg Ile Ala Ile Arg Tyr His Glu
                              730
Asp Asn Pro Pro Ala Leu Ala Val Arg Met Gln Glu Met Phe Gly Glu
  740 745
Ala Thr Asn Pro Thr Ile Ala Gln Gly Arg Val Pro Leu Val Leu Glu
                 760
Leu Leu Ser Pro Ala Gln Arg Pro Leu Gln Ile Thr Arg Asp Leu Ser
 770 775
Asp Phe Trp Lys Gly Ala Tyr Arg Glu Val Gln Lys Glu Met Lys Gly
                 790
                                  795
Arg Tyr Pro Lys His Val Trp Pro Asp Asp Pro Ala Asn Thr Ala Pro
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Thr Arg Arg Thr Lys Lys Tyr Ser
          820
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Val Ser Gly Thr Ser Leu Ile Ser Ser Leu Tyr Gly Asp Ser Leu Ser
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                            25
His Arg Gly Gly Glu Ile Trp Leu Gly Ser Leu Ala Ala Leu Leu Glu
                        40
Gly Leu Gly Phe Gly Glu Arg Phe Val Arg Thr Ala Leu Phe Arg Leu
                    55
Asn Lys Glu Gly Trp Leu Asp Val Ser Arg Ile Gly Arg Arg Ser Phe
                                  75
                70
Tyr Ser Leu Ser Asp Lys Gly Leu Arg Leu Thr Arg Arg Ala Glu Ser
                              90
Lys Ile Tyr Arg Ala Glu Gln Pro Ala Trp Asp Gly Lys Trp Leu Leu
                    105 110
Leu Leu Ser Glu Gly Leu Asp Lys Ser Thr Leu Ala Asp Val Lys Lys
                120 125
Gln Leu Ile Trp Gln Gly Phe Gly Ala Leu Ala Pro Ser Leu Met Ala
                    135
                                     140
Ser Pro Ser Gln Lys Leu Ala Asp Val Gln Thr Leu Leu His Glu Ala
                150
                                   155
Gly Val Ala Asp Asn Val Ile Cys Phe Glu Ala Gln Ile Pro Leu Ala
             165 . 170 175
Leu Ser Arg Ala Ala Leu Arg Ala Arg Val Glu Glu Cys Trp His Leu
          180
                           185
Thr Glu Gln Asn Ala Met Tyr Glu Thr Phe Ile Gln Ser Phe Arg Pro
                       200
Leu Val Pro Leu Leu Lys Glu Ala Ala Asp Glu Leu Thr Pro Glu Arg
                         220
                    215
Ala Phe His Ile Gln Leu Leu Leu Ile His Phe Tyr Arg Arg Val Val
                 230
                                  235
Leu Lys Asp Pro Leu Leu Pro Glu Glu Leu Leu Pro Ala His Trp Ala
                                                255
                              250
             245
Gly His Thr Ala Arg Gln Leu Cys Ile Asn Ile Tyr Gln Arg Val Ala
           260 265 270
Pro Ala Ala Leu Ala Phe Val Ser Glu Lys Gly Glu Thr Ser Val Gly
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280
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Glu Leu Pro Ala Pro Gly Ser Leu Tyr Phe Gln Arg Phe Gly Gly Leu
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Asn Ile Glu Gln Glu Ala Leu Cys Gln Phe Ile Arg
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Ser Phe Val His Pro Thr Ala Val Leu Ile Gly Asp Val Ile Leu Gly
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Lys Gly Val Tyr Val Gly Pro Asn Ala Ser Leu Arg Gly Asp Phe Gly
                           40
Arg Ile Val Val Lys Asp Gly Ala Asn Ile Gln Asp Asn Cys Val Met
                       55
His Gly Phe Pro Glu Gln Asp Thr Val Val Gly Glu Asp Gly His Ile
                  70
                                      75
Gly His Ser Ala Ile Leu His Gly Cys Ile Ile Arg Arg Asn Ala Leu
                                   90
Val Gly Met Asn Ala Val Val Met Asp Gly Ala Val Ile Gly Glu Asn
                              105
           100
Ser Ile Val Gly Ala Ser Ala Phe Val Lys Ala Lys Ala Glu Met Pro
                          120
                                              125
Ala Asn Tyr Leu Ile Val Gly Ser Pro Ala Lys Ala Ile Arg Glu Leu
                       135
                                           140
Ser Glu Gln Glu Leu Ala Trp Lys Lys Gln Gly Thr His Glu Tyr Gln
                   150
                                      155
Val Leu Val Thr Arg Cys Lys Gln Thr Leu His Gln Val Glu Pro Leu
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Arg Glu Ile Glu Pro Gly Arg Lys Arg Leu Val Phe Asp Glu Asn Leu
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Arg Pro Lys Gln
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Asn Gly Ile Tyr Ala Val Cys Ser Ala His Pro Leu Val Leu Glu Ala
                               25
            20
Ala Ile Arg Tyr Ala Ser Ala Asn Gln Thr Pro Leu Leu Ile Glu Ala
Thr Ser Asn Gln Val Asp Gln Phe Gly Gly Tyr Thr Gly Met Thr Pro
                                           60
Ala Asp Phe Arg Gly Phe Val Cys Gln Leu Ala Asp Ser Leu Asn Phe
                                       75
                   70
Pro Gln Asp Ala Leu Ile Leu Gly Gly Asp His Leu Gly Pro Asn Arg
                                   90
               85
Trp Gln Asn Leu Pro Ala Ala Gln Ala Met Ala Asn Ala Asp Asp Leu
                             105
Ile Lys Ser Tyr Val Ala Ala Gly Phe Lys Lys Ile His Leu Asp Cys
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125

```
120
      115
Ser Met Ser Cys Gln Asp Asp Pro Ile Pro Leu Thr Asp Asp Ile Val
                                      140
                    135
Ala Glu Arg Ala Ala Arg Leu Ala Lys Val Ala Glu Glu Thr Cys Leu
                                  155
                150
Glu His Phe Gly Glu Ala Asp Leu Glu Tyr Val Ile Gly Thr Glu Val
                       170
             165
Pro Val Pro Gly Gly Ala His Glu Thr Leu Ser Glu Leu Ala Val Thr
                  185
Thr Pro Asp Ala Ala Arg Ala Thr Leu Glu Ala His Arg His Ala Phe
              200
                                           205
Glu Lys Gln Gly Leu Asn Ala Ile Trp Pro Arg Ile Ile Ala Leu Val
           215
                                       220
Val Gln Pro Gly Val Glu Phe Asp His Thr Asn Val Ile Asp Tyr Gln
                      .
                                    235
               230
Pro Ala Lys Ala Ser Ala Leu Ser Gln Met Val Glu Asn Tyr Glu Thr
                                250
Leu Ile Phe Glu Ala His Ser Thr Asp Tyr Gln Thr Pro Gln Ser Leu
                            265
Arg Gln Leu Val Ile Asp His Phe Ala Ile Leu Lys Val Gly Pro Ala
                        280
                                           285
Leu Thr Phe Ala Leu Arg Glu Ala Leu Phe Ser Leu Ala Ala Ile Glu
                           300
                    295
Glu Glu Leu Val Pro Ala Lys Ala Cys Ser Gly Leu Arg Gln Val Leu
                                   315
                 310 .
Glu Asp Val Met Leu Asp Arg Pro Glu Tyr Trp Gln Ser His Tyr His
                                330
              325
Gly Asp Gly Asn Ala Arg Arg Leu Ala Arg Gly Tyr Ser Tyr Ser Asp
          340
                            345
                                               350
Arg Val Arg Tyr Tyr Trp Pro Asp Ser Gln Ile Asp Asp Ala Phe Ala
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His Leu Val Arg Asn Leu Ala Asp Ser Pro Ile Pro Leu Pro Leu Ile
                                       380
                     375
Ser Gln Tyr Leu Pro Leu Gln Tyr Val Lys Val Arg Ser Gly Glu Leu
                                 395
         390
Gln Pro Thr Pro Arg Glu Leu Ile Ile Asn His Ile Gln Asp Ile Leu
                                410
              405
Ala Gln Tyr His Thr Ala Cys Glu Gly Gln
<210> 381
<211> 169
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Met Lys Ala Asn Lys Gln Asn Lys Glu Glu His Ala Met Pro Asn Ile
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Val Leu Ser Arg Ile Asp Glu Arg Leu Ile His Gly Gln Val Gly Val
                             25 ·
           20
Gln Trp Val Gly Phe Ala Gly Ala Asn Leu Val Leu Val Ala Asn Asp
                                  . 45
              40
Glu Val Ala Glu Asp Pro Val Gln Gln Asn Leu Met Glu Met Val Leu
                   - 55
                                       60
Ala Glu Gly Ile Ala Val Arg Phe Trp Thr Leu Gln Lys Val Ile Asp
                                    75
                  70
Asn Ile His Arg Ala Ala Asp Arg Gln Lys Ile Leu Leu Val Cys Lys
              85
                                90
Thr Pro Ala Asp Phe Leu Thr Leu Val Lys Gly Gly Val Pro Val Asn
                             105
           100
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Arg Ile Asn Val Gly Asn Met His Tyr Ala Asn Gly Lys Gln Gln Ile 120 Ala Lys Thr Val Ser Val Asp Ala Gly Asp Ile Ala Ala Phe Asn Asp 135 140 Leu Lys Thr Ala Gly Val Glu Cys Phe Val Gln Gly Val Pro Thr Glu 150 155 Pro Ala Val Asp Leu Phe Lys Leu Leu 165 <210> 382 <211> 133 <212> PRT <213> Escherichia coli <400> 382 Met Glu Ile Ser Leu Leu Gln Ala Phe Ala Leu Gly Ile Ile Ala Phe 10 Ile Ala Gly Leu Asp Met Phe Asn Gly Leu Thr His Met His Arg Pro 25 Val Val Leu Gly Pro Leu Val Gly Leu Val Leu Gly Asp Leu His Thr 40 45 Gly Ile Leu Thr Gly Gly Thr Leu Glu Leu Val Trp Met Gly Leu Ala 55 Pro Leu Ala Gly Ala Gln Pro Pro Asn Val Ile Ile Gly Thr Ile Val Gly Thr Ala Phe Ala Ile Thr Thr Gly Val Lys Pro Asp Val Ala Val 90 85 Gly Val Ala Val Pro Phe Ala Val Ala Val Gln Met Gly Ile Thr Phe 100 105 Leu Phe Ser Val Met Ser Gly Val Met Ser Arg Cys Asp Leu Ala Thr 120 115 Asn Pro Arg Arg Ile 130 <210> 383 <211> 167 <212> PRT <213> Escherichia coli <400> 383 Met His Cys Tyr Asn Gly Met Thr Gly Leu His His Arg Glu Pro Gly 10 Met Val Gly Ala Gly Leu Thr Asp Lys Arg Ala Trp Leu Glu Leu Ile 25 Ala Asp Gly His His Val His Pro Ala Ala Met Ser Leu Cys Cys Cys Ala Lys Glu Arg Ile Val Leu Ile Thr Asp Ala Met Gln Ala Ala 55 60 Gly Met Pro Asp Gly Arg Tyr Thr Leu Cys Gly Glu Glu Val Gln Met 75 70 His Gly Gly Val Val Arg Thr Ala Ser Gly Gly Leu Ala Gly Ser Thr 90 85 Leu Ser Val Asp Ala Ala Val Arg Asn Met Val Glu Leu Thr Gly Val 105 Thr Pro Ala Glu Ala Ile His Met Ala Ser Leu His Pro Ala Arg Met 120 125 Leu Gly Val Asp Gly Val Leu Gly Ser Leu Lys Pro Gly Lys Arg Ala 135 140 Arg Val Val Ala Leu Asp Ser Gly Leu His Val Gln Gln Ile Trp Ile 155

Gln Gly Gln Leu Ala Ser Phe 165

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<210> 385 <211> 286

Thr Val Asn Arg Val Val Gln Gly Val Ile Ile His Pro Trp Gln Ala

375

<212> PRT <213> Escherichia coli <400> 385 Met Ser Ile Ile Ser Thr Lys Tyr Leu Leu Gln Asp Ala Gln Ala Asn Gly Tyr Ala Val Pro Ala Phe Asn Ile His Asn Ala Glu Thr Ile Gln 25 Ala Ile Leu Glu Val Cys Ser Glu Met Arg Ser Pro Val Ile Leu Ala 40 Gly Thr Pro Gly Thr Phe Lys His Ile Aka Leu Glu Glu Ile Tyr Ala Leu Cys Ser Ala Tyr Ser Thr Thr Tyr Asn Met Pro Leu Ala Leu His 70 75 Leu Asp His His Glu Ser Leu Asp Asp Ile Arg Arg Lys Val His Ala 90 85 Gly Val Arg Ser Ala Met Ile Asp Gly Ser His Phe Pro Phe Ala Glu 105 Asn Val Lys Leu Val Lys Ser Val Val Asp Phe Cys His Ser Gln Asp 120 115 Cys Ser Val Glu Ala Glu Leu Gly Arg Leu Gly Gly Val Glu Asp Asp 135 140 Met Ser Val Asp Ala Glu Ser Ala Phe Leu Thr Asp Pro Gln Glu Ala 155 150 Lys Arg Phe Val Glu Leu Thr Gly Val Asp Ser Leu Ala Val Ala Ile. 170 Gly Thr Ala His Gly Leu Tyr Ser Lys Thr Pro Lys Ile Asp Phe Gln 185 Arg Leu Ala Glu Ile Arg Glu Val Val Asp Val Pro Leu Val Leu His 200 Gly Ala Ser Asp Val Pro Asp Glu Phe Val Arg Arg Thr Ile Glu Leu 215 220 Gly Val Thr Lys Val Asn Val Ala Thr Glu Leu Lys Ile Ala Phe Ala 235 230 Gly Ala Val Lys Ala Trp Phe Ala Glu Asn Pro Gln Gly Asn Asp Pro 250 245 Arg Tyr Tyr Met Arg Val Gly Met Asp Ala Met Lys Glu Val Val Arg 265 260 Asn Lys Ile Asn Val Cys Gly Ser Ala Asn Arg Ile Ser Ala <210> 386 <211> 118 <212> PRT <213> Escherichia coli <400> 386 Met Ala Arg Ile Ala Gly Ile Asn Ile Pro Asp His Lys His Ala Val 10 Ile Ala Leu Thr Ser Ile Tyr Gly Val Gly Lys Thr Arg Ser Lys Ala 25 Ile Leu Ala Ala Ala Gly Ile Ala Glu Asp Val Lys Ile Ser Glu Leu 40 Ser Glu Gly Gln Ile Asp Thr Leu Arg Asp Glu Val Ala Lys Phe Val Val Glu Gly Asp Leu Arg Arg Glu Ile Ser Met Ser Ile Lys Arg Leu 70 75 Met Asp Leu Gly Cys Tyr Arg Gly Leu Arg His Arg Arg Gly Leu Pro 85 90

Val Arg Gly Gln Arg Thr Lys Thr Asn Ala Arg Thr Arg Lys Gly Pro

110 100 105 Arg Lys Pro Ile Lys Lys <210> 387 <211> 129 <212> PRT <213> Escherichia coli <400> 387 Met Ala Lys Ala Pro Ile Arg Ala Arg Lys Arg Val Arg Lys Gln Val 10 Ser Asp Gly Val Ala His Ile His Ala Ser Phe Asn Asn Thr Ile Val Thr Ile Thr Asp Arg Gln Gly Asn Ala Leu Gly Trp Ala Thr Ala Gly 40 45 Gly Ser Gly Phe Arg Gly Ser Arg Lys Ser Thr Pro Phe Ala Ala Gln 55 Val Ala Ala Glu Arg Cys Ala Asp Ala Val Lys Glu Tyr Gly Ile Lys Asn Leu Glu Val Met Val Lys Gly Pro Gly Pro Gly Arg Glu Ser Thr . 90 Ile Arg Ala Leu Asn Ala Ala Gly Phe Arg Ile Thr Asn Ile Thr Asp 105 110 Val Thr Pro Ile Pro His Asn Gly Cys Arg Pro Pro Lys Lys Arg Arg Val <210> 388 <211> 206 <212> PRT <213> Escherichia coli <400> 388 Met Ala Arg Tyr Leu Gly Pro Lys Leu Lys Leu Ser Arg Arg Glu Gly Thr Asp Leu Phe Leu Lys Ser Gly Val Arg Ala Ile Asp Thr Lys Cys 25 Lys Ile Glu Gln Ala Pro Gly Gln His Gly Ala Arg Lys Pro Arg Leu 45 Ser Asp Tyr Gly Val Gln Leu Arg Glu Lys Gln Lys Val Arg Arg Ile Tyr Gly Val Leu Glu Arg Gln Phe Arg Asn Tyr Tyr Lys Glu Ala Ala 70 75 Arg Leu Lys Gly Asn Thr Gly Glu Asn Leu Leu Ala Leu Leu Glu Gly 90 Arg Leu Asp Asn Val Val Tyr Arg Met Gly Phe Gly Ala Thr Arg Ala 105 110 Glu Ala Arg Gln Leu Val Ser His Lys Ala Ile Met Val Asn Gly Arg 120 Val Val Asn Ile Ala Ser Tyr Gln Val Ser Pro Asn Asp Val Val Ser 135 140 Ile Arg Glu Lys Ala Lys Lys Gln Ser Arg Val Lys Ala Ala Leu Glu 150 155 Leu Ala Glu Gln Arg Glu Lys Pro Thr Trp Leu Glu Val Asp Ala Gly 170 165 Lys Met Glu Gly Thr Phe Lys Arg Lys Pro Glu Arg Ser Asp Leu Ser

180 185 190
Ala Asp Ile Asn Glu His Leu Ile Val Glu Leu Tyr Ser Lys

205

200

195

<210> 389 <211> 329 <212> PRT <213> Escherichia coli <400> 389 Met Gln Gly Ser Val Thr Glu Phe Leu Lys Pro Arg Leu Val Asp Ile 10 Glu Gln Val Ser Ser Thr His Ala Lys Val Thr Leu Glu Pro Leu Glu 25 Arg Gly Phe Gly His Thr Leu Gly Asn Ala Leu Arg Arg Ile Leu Leu 40 Ser Ser Met Pro Gly Cys Ala Val Thr Glu Val Glu Ile Asp Gly Val Leu His Glu Tyr Ser Thr Lys Glu Gly Val Gln Glu Asp Ile Leu Glu 70 75 . 80 Ile Leu Leu Asn Leu Lys Gly Leu Ala Val Arg Val Gln Gly Lys Asp 85 Glu Val Ile Leu Thr Leu Asn Lys Ser Gly Ile Gly Pro Val Thr Ala 105 Ala Asp Ile Thr His Asp Gly Asp Val Glu Ile Val Lys Pro Gln His 120 125 Val Ile Cys His Leu Thr Asp Glu Asn Ala Ser Ile Ser Met Arg Ile 135 140 Lys Val Gln Arg Gly Arg Gly Tyr Val Pro Ala Ser Thr Arg Ile His 150 155 Ser Glu Glu Asp Glu Arg Pro Ile Gly Arg Leu Leu Val Asp Ala Cys 170 165 Tyr Ser Pro Val Glu Arg Ile Ala Tyr Asn Val Glu Ala Ala Arg Val 185 Glu Gln Arg Thr Asp Leu Asp Lys Leu Val Ile Glu Met Glu Thr Asn 205 200 Gly Thr Ile Asp Pro Glu Glu Ala Ile Arg Arg Ala Ala Thr Ile Leu 215 220 Ala Glu Gln Leu Glu Ala Phe Val Asp Leu Arg Asp Val Arg Gln Pro 230 235 Glu Val Lys Glu Glu Lys Pro Glu Phe Asp Pro Ile Leu Leu Arg Pro 245 250 255 Val Asp Asp Leu Glu Leu Thr Val Arg Ser Ala Asn Cys Leu Lys Ala 265 Glu Ala Ile His Tyr Ile Gly Asp Leu Val Gln Arg Thr Glu Val Glu 280 Leu Leu Lys Thr Pro Asn Leu Gly Lys Lys Ser Leu Thr Glu Ile Lys 295 300 Asp Val Leu Ala Ser Arg Gly Leu Ser Leu Gly Met Arg Leu Glu Asn 310 315 Trp Pro Pro Ala Ser Ile Ala Asp Glu 325 <210> 390 <211> 127 <212> PRT <213> Escherichia coli <400> 390 Met Arg His Arg Lys Ser Gly Arg Gln Leu Asn Arg Asn Ser Ser His 10

Arg Gln Ala Met Phe Arg Asn Met Ala Gly Ser Leu Val Arg His Glu

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25
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Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val
                          40
Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg
                       55
Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe
                                    75
                   70
Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg
Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr
                              105
Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu
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<211> 243
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Ala Leu Ile Phe Trp Leu Pro Tyr Ser Gln Pro Leu Phe Ala Ala Leu
Phe Pro Gln Leu Pro Arg Pro Val Tyr Gln Gln Glu Ser Phe Ala Ala
Leu Ala Leu Ala His Phe Trp Leu Val Gly Ile Ser Ser Leu Phe Ala
                       55
Val Ile Ile Gly Thr Gly Ala Gly Ile Ala Val Thr Arg Pro Trp Gly
                                       75
Ala Glu Phe Arg Pro Leu Val Glu Thr Ile Ala Ala Val Gly Gln Thr
Phe Pro Pro Val Ala Val Leu Ala Ile Ala Val Pro Val Ile Gly Phe
                               105
Gly Leu Gln Pro Ala Ile Ile Ala Leu Ile Leu Tyr Gly Val Leu Pro
                                              125
                           120
Val Leu Gln Ala Thr Leu Ala Gly Leu Gly Ala Ile Asp Ala Ser Val
                      1.35
Thr Glu Val Ala Lys Gly Met Gly Met Ser Arg Gly Gln Arg Val Arg
                   150
                                       155
Lys Val Glu Leu Pro Leu Ala Ala Pro Val Ile Leu Ala Gly Val Arg
               165
                                   170
Thr Ser Val Ile Ile Asn Ile Gly Thr Ala Thr Ile Ala Ser Thr Val
                                185
Gly Ala Ser Thr Leu Gly Thr Pro Ile Ile Ile Gly Leu Ser Gly Phe
                           200
Asn Thr Ala Tyr Val Ile Gln Gly Ala Leu Leu Val Ala Leu Ala Ala
                                           220
                       215
Ile Ile Ala Asp Arg Leu Phe Glu Arg Leu Val Gln Ala Leu Ser Gln
                    230
                                       235
His Ala Lys
<210> 392
<211> 308
<212> PRT
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Met Ile Glu Phe Ser His Val Ser Lys Leu Phe Gly Ala Gln Lys Ala

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Val Asn Asp Leu Asn Leu Asn Phe Gln Glu Gly Ser Phe Ser Val Leu
                              25
Ile Gly Thr Ser Gly Ser Gly Lys Ser Thr Thr Leu Lys Met Ile Asn
                           40
Arg Leu Val Glu His Asp Ser Gly Glu Ile Arg Phe Ala Gly Glu Glu
Ile Arg Ser Leu Pro Val Leu Glu Leu Arg Arg Arg Met Gly Tyr Ala
                   70
Ile Gln Ser Ile Gly Leu Phe Pro His Trp Ser Val Ala Gln Asn Ile
                                  90
               85
Ala Thr Val Pro Gln Leu Gln Lys Trp Ser Arg Ala Arg Ile Asp Asp
                              105
           100
Arg Ile Asp Glu Leu Met Ala Leu Leu Gly Leu Glu Ser Asn Leu Arg
                           120
                                              125
Glu Arg Tyr Pro His Gln Leu Ser Gly Gly Gln Gln Gln Arg Val Gly
                      135
                                          140
Val Ala Arg Ala Leu Ala Ala Asp Pro Gln Val Leu Leu Met Asp Glu
                  150
                                       155
Pro Phe Gly Ala Leu Asp Pro Val Thr Arg Gly Ala Leu Gln Glu
                                   170
Met Thr Arg Ile His Arg Leu Leu Gly Arg Thr Ile Val Leu Val Thr
                               185
His Asp Ile Asp Glu Ala Leu Arg Leu Ala Glu His Leu Val Leu Met
                           200
Asp His Gly Glu Val Val Gln Gln Gly Asn Pro Leu Thr Met Leu Thr
                                           220
                       215
Arg Pro Ala Asn Asp Phe Val Arg Gln Phe Phe Gly Arg Ser Glu Leu
                                      235
                  230
Gly Val Arg Leu Leu Ser Leu Arg Ser Val Ala Asp Tyr Val Arg Arg
                                  250
               245
Glu Glu Arg Ala Asp Gly Glu Ala Leu Ala Glu Glu Met Thr Leu Arg
                               265
           260
Asp Ala Leu Ser Leu Phe Val Ala Arg Gly Cys Glu Val Leu Pro Val
                           280
                                              285
Val Asn Met Gln Gly Gln Pro Cys Gly Thr Leu His Phe Gln Asp Leu
                      295
Leu Val Glu Ala
305
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Met Thr Tyr Phe Arg Ile Asn Pro Val Leu Ala Leu Leu Leu Leu
Thr Ala Ile Ala Ala Ala Leu Pro Phe Ile Ser Tyr Ala Pro Asn Arg
                                25
Leu Val Ser Gly Glu Gly Arg His Leu Trp Gln Leu Trp Pro Gln Thr
                            40
Ile Trp Met Leu Val Gly Val Gly Cys Ala Trp Leu Thr Ala Cys Phe
Ile Pro Gly Lys Lys Gly Ser Ile Cys Ala Leu Ile Leu Ala Gln Phe
                                        75
Val Phe Val Leu Leu Val Trp Gly Ala Gly Lys Ala Ala Thr Gln Leu
                                    90
Ala Gln Asn Gly Ser Ala Leu Ala Arg Thr Ser Leu Gly Ser Gly Phe
                                105
            100
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Trp Leu Ala Ala Ala Leu Ala Leu Leu Ala Cys Ser Asp Ala Ile Arg
                              125
             120
  115
Arg Ile Ser Thr His Pro Leu Trp Arg Trp Leu Leu His Met Gln Ile
                                    140
                    135
Ala Ile Ile Pro Leu Trp Leu Leu Tyr Ser Gly Thr Leu Asn Asp Leu
         150 155
Ser Leu Met Lys Glu Tyr Ala Asn Arg Gln Asp Val Phe Asp Asp Ala
                                170
            165
Leu Ala Gln His Leu Thr Leu Leu Phe Gly Ala Val Leu Pro Ala Leu
    180
                            185
Val Ile Gly Val Pro Leu Gly Ile Trp Cys Tyr Phe Ser Thr Ala Arg
                         200
Gln Gly Ala Ile Phe Ser Leu Leu Asn Val Ile Gln Thr Val Pro Ser
                                      220
           215
Val Ala Leu Phe Gly Leu Leu Ile Ala Pro Leu Ala Ala Leu Val Thr
                 230
Ala Phe Pro Trp Leu Gly Thr Leu Gly Ile Ala Gly Thr Gly Met Thr
                               250
Pro Ala Leu Ile Ala Leu Val Leu Tyr Ala Leu Leu Pro Leu Val Arg
                         265 .
Gly Val Val Val Gly Leu Asn Gln Ile Pro Arg Asp Val Leu Glu Ser
              280
Ala Arg Ala Met Gly Met Ser Gly Ala Gln Arg Phe Leu His Val Gln
  290 . 295
                                       300
Leu Pro Leu Ala Leu Pro Val Phe Leu Arg Ser Leu Arg Val Val Met
                                   315
                 310
Val Gln Thr Val Gly Met Ala Val Ile Ala Ala Leu Ile Gly Ala Gly
                               330
              325
Gly Phe Gly Ala Leu Val Phe Gln Gly Leu Leu Ser Ser Ala Ile Asp
                   345
          340
Leu Val Leu Leu Gly Val Ile Pro Val Ile Val Leu Ala Val Leu Thr
                        360
                                  365
Asp Ala Leu Phe Asp Leu Leu Ile Ala Leu Leu Lys Val Lys Arg Asn
                  375
Asp
385
<210> 394
<211> 305
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<213> Escherichia coli
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Met Pro Leu Leu Lys Leu Trp Ala Gly Ser Leu Val Met Leu Ala Ala
Val Ser Leu Pro Leu Gln Ala Ala Ser Pro Val Lys Val Gly Ser Lys
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Ile Asp Thr Glu Gly Ala Leu Leu Gly Asn Ile Ile Leu Gln Val Leu
                      . 40.
Glu Ser His Gly Val Pro Thr Val Asn Lys Val Gln Leu Gly Thr Thr
                     55
Pro Val Val Arg Gly Ala Ile Thr Ser Gly Glu Leu Asp Ile Tyr Pro
                                    75
                  70
Glu Tyr Thr Gly Asn Gly Ala Phe Phe Phe Lys Asp Glu Asn Asp Ala
                              . 90
Ala Trp Lys Asn Ala Gln Gln Gly Tyr Glu Lys Val Lys Lys Leu Asp
                             105
Ser Glu His Asn Lys Leu Ile Trp Leu Thr Pro Ala Pro Ala Asn Asn
            120
                                 125
Thr Trp Thr Ile Ala Val Arg Gln Asp Val Ala Glu Lys Asn Lys Leu
```

```
135
                                         140
Thr Ser Leu Ala Asp Leu Ser Arg Tyr Leu Gln Glu Gly Gly Thr Phe
                  150
                                     155
Lys Leu Ala Ala Ser Ala Glu Phe Ile Glu Arg Ala Asp Ala Leu Pro
              165
                                  170
Ala Phe Glu Lys Ala Tyr Gly Phe Lys Leu Gly Gln Asp Gln Leu Leu
                              185
Ser Leu Ala Gly Gly Asp Thr Ala Val Thr Ile Lys Ala Ala Ala Gln
                        200
      195
Gln Thr Ser Gly Val Asn Ala Ala Met Ala Tyr Gly Thr Asp Gly Pro
                                         220
                     215
Val Ala Ala Leu Gly Leu Gln Thr Leu Ser Asp Pro Gln Gly Val Gln
                            235
                 230
Pro Ile Tyr Ala Pro Ala Pro Val Val Arg Glu Ser Val Leu Arg Glu
                       250
              245
Tyr Pro Gln Met Ala Gln Trp Leu Gln Pro Val Phe Ala Ser Leu Asp
                                                  270
          260
                              265
Ala Lys Thr Leu Gln Gln Leu Asn Ala Ser Ile Ala Val Glu Gly Leu
                           280
Asp Ala Lys Lys Val Ala Ala Asp Tyr Leu Lys Gln Lys Gly Trp Thr
                       295
Lys
305
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<211> 207
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<213> Escherichia coli
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Met Leu Val Tyr Trp Leu Asp Ile Val Gly Thr Ala Val Phe Ala Ile
Ser Gly Val Leu Leu Ala Gly Lys Leu Arg Met Asp Pro Phe Gly Val
Leu Val Leu Gly Val Val Thr Ala Val Gly Gly Gly Thr Ile Arg Asp
                          40
Met Ala Leu Asp His Gly Pro Val Phe Trp Val Lys Asp Pro Thr Asp
                       55
Leu Val Val Ala Met Val Thr Ser Met Leu Thr Ile Val Leu Val Arg
                   70
                                     75
Gln Pro Arg Arg Leu Pro Lys Trp Met Leu Pro Val Leu Asp Ala Val
                                  90
              85
Gly Leu Ala Val Phe Val Gly Ile Gly Val Asn Lys Ala Phe Asn Ala
                              105
          100
Glu Ala Gly Pro Leu Ile Ala Val Cys Met Gly Val Ile Thr Gly Val
                                              125
                           120
     115
Gly Gly Gly Ile Ile Arg Asp Val Leu Ala Arg Glu Ile Pro Met Ile
                                          140
                       135
Leu Arg Thr Glu Ile Tyr Ala Thr Ala Cys Ile Ile Gly Gly Ile Val
                                      155
                   150
His Ala Thr Ala Tyr Tyr Thr Phe Ser Val Pro Leu Glu Thr Ala Ser
                                  170
               165
Met Met Gly Met Val Val Thr Leu Leu Ile Arg Leu Ala Ala Ile Arg
                              185
Trp His Leu Lys Leu Pro Thr Phe Ala Leu Asp Glu Asn Gly Arg
                           200
<210> 396
<211> 266
<212> PRT
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-358-

<213> Escherichia coli

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<210> 397

<211> 232

<212> PRT

<213> Escherichia coli

<400> 397

 Met Lys
 Ile Gly Ile Gly Ile Gly Ala Met Glu Glu Glu Val Thr Leu Leu 1
 5
 10
 15
 15

 Arg Asp Lys
 Ile Glu Asn Arg Gln Thr Ile Ser Leu Gly Gly Cys Glu 20
 20
 30
 30
 30

 Ile Tyr Thr Gly Gln Leu Asn Gly Thr Glu Val Ala Leu Leu Leu Leu Leu Gly Ile Gly Ile Gly Lys Val Ala Ala Ala Leu Gly Ala Thr Leu Leu Leu Glu 50
 40
 45
 60
 60

 His Cys Lys Pro Asp Val Ile Ile Asn Thr Gly Ser Ala Gly Gly Leu 65
 70
 75
 80

 Ala Pro Thr Leu Lys Val Gly Asp Ile Val Val Ser Asp Glu Ala Arg 85
 90
 95

 Tyr His Asp Ala Asp Ala Asp Val Thr Ala Phe Gly Tyr Glu Tyr Gly Gln Leu 100
 105
 110

 Pro Gly Cys Pro Ala Gly Phe Lys Ala Asp Asp Lys Leu Ile Ala Ala

120

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Ala Glu Ala Cys Ile Ala Glu Leu Asn Leu Asn Ala Val Arg Gly Leu
                     135
                                          140
Ile Val Ser Gly Asp Ala Phe Ile Asn Gly Ser Val Gly Leu Ala Lys
                   150
                                       155
Ile Arq His Asn Phe Pro Gln Ala Ile Ala Val Glu Met Glu Ala Thr
               165
                                  170
Ala Ile Ala His Val Cys His Asn Phe Asn Val Pro Phe Val Val Val
           180
                              185
Arg Ala Ile Ser Asp Val Ala Asp Gln Gln Ser His Leu Ser Phe Asp
                          200
Glu Phe Leu Ala Val Ala Ala Lys Gln Ser Ser Leu Met Val Glu Ser
Leu Val Gln Lys Leu Ala His Gly
                   230
<210> 398
<211> 262
<212> PRT
<213> Escherichia coli
<400> 398
Met Ile Asp Lys Ser Ala Phe Val His Pro Thr Ala Ile Val Glu Glu
                                   10
1
Gly Ala Ser Ile Gly Ala Asn Ala His Ile Gly Pro Phe Cys Ile Val
                               25
Gly Pro His Val Glu Ile Gly Glu Gly Thr Val Leu Lys Ser His Val
                          40
Val Val Asn Gly His Thr Lys Ile Gly Arg Asp Asn Glu Ile Tyr Gln
                      55
Phe Ala Ser Ile Gly Glu Val Asn Gln Asp Leu Lys Tyr Ala Gly Glu
                    70
Pro Thr Arg Val Glu Ile Gly Asp Arg Asn Arg Ile Arg Glu Ser Val
Thr Ile His Arg Gly Thr Val Gln Gly Gly Gly Leu Thr Lys Val Gly
           100
                              105
Ser Asp Asn Leu Leu Met Ile Asn Ala His Ile Ala His Asp Cys Thr
       115
                          120
Val Gly Asn Arg Cys Ile Leu Ala Asn Asn Ala Thr Leu Ala Gly His
                      135
Val Ser Val Asp Asp Phe Ala Ile Ile Gly Gly Met Thr Ala Val His
                  150
                                      155
Gln Phe Cys Ile Ile Gly Ala His Val Met Val Gly Gly Cys Ser Gly
                                  170
              165
Val Ala Gln Asp Val Pro Pro Tyr Val Ile Ala Gln Gly Asn His Ala
                               185
Thr Pro Phe Gly Val Asn Ile Glu Gly Leu Lys Arg Arg Gly Phe Ser
                            200
Arg Glu Ala Ile Thr Ala Ile Arg Asn Ala Tyr Lys Leu Ile Tyr Arg
                                           220
                       215
Ser Gly Lys Thr Leu Asp Glu Val Lys Pro Glu Ile Ala Glu Leu Ala
                                       235
                   230
Glu Thr Tyr Pro Glu Val Lys Ala Phe Thr Asp Phe Phe Ala Arg Ser
Thr Arg Gly Leu Ile Arg
            260
<210> 399
<211> 382
<212> PRT
<213> Escherichia coli
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Ser Gly Asp Ile Leu Gly Ala Gly Leu Ile Arg Ala Leu Lys Glu His
Val Pro Asn Ala Arg Phe Val Gly Val Ala Gly Pro Arg Met Gln Ala
Glu Gly Cys Glu Ala Trp Tyr Glu Met Glu Glu Leu Ala Val Met Gly
                      55
Ile Val Glu Val Leu Gly Arg Leu Arg Arg Leu Leu His Ile Arg Ala
                                     75
                70
Asp Leu Thr Lys Arg Phe Gly Glu Leu Lys Pro Asp Val Phe Val Gly
                                  90
              85
Ile Asp Ala Pro Asp Phe Asn Ile Thr Leu Glu Gly Asn Leu Lys Lys
                            105
Gln Gly Ile Lys Thr Ile His Tyr Val Ser Pro Ser Val Trp Ala Trp
                                            125
                          120
Arg Gln Lys Arg Val Phe Lys Ile Gly Arg Ala Thr Asp Leu Val Leu
                                        140
                     135
Ala Phe Leu Pro Phe Glu Lys Ala Phe Tyr Asp Lys Tyr Asn Val Pro
                                     155
        150
Cys Arg Phe Ile Gly His Thr Met Ala Asp Ala Met Pro Leu Asp Pro
                                 170
              165
Asp Lys Asn Ala Ala Arg Asp Val Leu Gly Ile Pro His Asp Ala His
                           185
Cys Leu Ala Leu Leu Pro Gly Ser Arg Gly Ala Glu Val Glu Met Leu
                          200
Ser Ala Asp Phe Leu Lys Thr Ala Gln Leu Leu Arg Gln Thr Tyr Pro
                      215
                                         220
Asp Leu Glu Ile Val Val Pro Leu Val Asn Ala Lys Arg Arg Glu Gln
                 230
                                   235
Phe Glu Arg Ile Lys Ala Glu Val Ala Pro Asp Leu Ser Val His Leu
              245
                                 250
Leu Asp Gly Met Gly Arg Glu Ala Met Val Ala Ser Asp Ala Ala Leu
                              265
Leu Ala Ser Gly Thr Ala Ala Leu Glu Cys Met Leu Ala Lys Cys Pro
                           280
Met Val Val Gly Tyr Arg Met Lys Pro Phe Thr Phe Trp Leu Ala Lys
                                          300
                       295
Arg Leu Val Lys Thr Asp Tyr Val Ser Leu Pro Asn Leu Leu Ala Gly
                                     315
                  310
Arg Glu Leu Val Lys Glu Leu Leu Gln Glu Glu Cys Glu Pro Gln Lys
              325
                                  330
Leu Ala Ala Ala Leu Leu Pro Leu Leu Ala Asn Gly Lys Thr Ser His
                              345
Ala Met His Asp Thr Phe Arg Glu Leu His Gln Gln Ile Arg Cys Asn
                         360
Ala Asp Glu Gln Ala Ala Gln Ala Val Leu Glu Leu Ala Gln
                      375
   370
<210> 400
<211> 198
<212> PRT
<213> Escherichia coli
Met Ile Glu Phe Val Tyr Pro His Thr Gln Leu Val Ala Gly Val Asp
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Glu Val Gly Arg Gly Pro Leu Val Gly Ala Val Val Thr Ala Ala Val

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20
                               25
Ile Leu Asp Pro Ala Arg Pro Ile Ala Gly Leu Asn Asp Ser Lys Lys
Leu Ser Glu Lys Arg Arg Leu Ala Leu Tyr Glu Glu Ile Lys Glu Lys
                       55
Ala Leu Ser Trp Ser Leu Gly Arg Ala Glu Pro His Glu Ile Asp Glu
                   70
Leu Asn Ile Leu His Ala Thr Met Leu Ala Met Gln Arg Ala Val Ala
   · 85
Gly Leu His Ile Ala Pro Glu Tyr Val Leu Ile Asp Gly Asn Arg Cys
                              105
Pro Lys Leu Pro Met Pro Ala Met Ala Val Val Lys Gly Asp Ser Arg
                          120
                                             125
Val Pro Glu Ile Ser Ala Ala Ser Ile Leu Ala Lys Val Thr Arg Asp
            135
                                         140
Ala Glu Met Ala Ala Leu Asp Ile Val Phe Pro Gln Tyr Gly Phe Ala
                   150
                                      155
Gln His Lys Gly Tyr Pro Thr Ala Phe His Leu Glu Lys Leu Ala Glu
               165
                        170
His Gly Ala Thr Glu His His Arg Arg Ser Phe Gly Pro Val Lys Arg
                              185
           180
Ala Leu Gly Leu Ala Ser
    195
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<212> PRT
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Met Ser Glu Pro Arg Phe Val His Leu Arg Val His Ser Asp Tyr Ser
Met Ile Asp Gly Leu Ala Lys Thr Ala Pro Leu Val Lys Lys Ala Ala
Ala Leu Gly Met Pro Ala Leu Ala Ile Thr Asp Phe Thr Asn Leu Cys
                          40
       35
Gly Leu Val Lys Phe Tyr Gly Ala Gly His Gly Ala Gly Ile Lys Pro
Ile Val Gly Ala Asp Phe Asn Val Gln Cys Asp Leu Leu Gly Asp Glu
                   70
                                       75
Leu Thr His Leu Thr Val Leu Ala Ala Asn Asn Thr Gly Tyr Gln Asn
             85
                                  90
Leu Thr Leu Leu Ile Ser Lys Ala Tyr Gln Arg Gly Tyr Gly Ala Ala
                               105
Gly Pro Ile Ile Asp Arg Asp Trp Leu Ile Glu Leu Asn Glu Gly Leu
                           120
Ile Leu Leu Ser Gly Gly Arg Met Gly Asp Val Gly Arg Ser Leu Leu
                                          140
                       135
Arg Gly Asn Ser Ala Leu Val Asp Glu Cys Val Ala Phe Tyr Glu Glu
                                      155
                   150
His Phe Pro Asp Arg Tyr Phe Leu Glu Leu Ile Arg Thr Gly Arg Pro
                                   170
Asp Glu Glu Ser Tyr Leu His Ala Ala Val Glu Leu Ala Glu Ala Arg
                              185
Gly Leu Pro Val Val Ala Thr Asn Asp Val Arg Phe Ile Asp Ser Ser
                          200
Asp Phe Asp Ala His Glu Ile Arg Val Ala Ile His Asp Gly Phe Thr
                      215
                                          220
Leu Asp Asp Pro Lys Arg Pro Arg Asn Tyr Ser Pro Gln Gln Tyr Met
                                       235
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Arg	Ser	Glu	Glu	Glu 245	Met	Cys	Glu	Leu	Phe 250	Ala	Asp	Ile	Pro	Glu 255	Ala
Leu	Ala	Asn	Thr 260		Glu	Ile	Ala	Lys 265	_	Суз	Asn	Val	Thr 270		Arg
Leu	Gly	Glu 275	Tyr	Phe	Leu	Pro	Gln 280	_	Pro	Thr	Gly	Asp 285		Ser	Thr
Glu	Asp 290		Leu	Val	Lys	Arg 295	Ala	Lys	Glu	Gly	Leu 300	Glu	Glu	Arg	Leu
305			Phe		310		•			315					320
-	_		Arg	325					330					335	
		_	Tyr 340					345					350		
		355	Val				360					365			
	370		Tyr			375					380				
385	Leu	Leu	Phe	GIU	390	Pne	теп	ASII	PIO	395	Arg	vai	ser	Mec	400
-		_	Val	405					410					415	
			Asp 420					425					430		
	_	435	Met				440					445			
	450		Pro			455			=		460				
Pro 465	Asp	Pro	Gly	Met	170	Leu	Ala	ьys	Ala	475	GIU	ALA	GIU	Pro	480
			Ile	485					490					495	
			Lys 500					505					510		
_	_	515	Val				520					525			
_	530		Glu			535					540				
545			Tyr		550					555					560
			Ile	565					570					575	
	-		Gly 580					585					590		•
_	_	595					600					605			Val
	610		Glu			615					620				·
625	_		Phe		630					635		•			640
_			Gln	645				•	650					655	
_			660					665					670		Ser
	_	675					680					685			Glu
	690					695					700				Gly
705	Asp	мес	ren	Arg	710	HIG	net	GTÀ	пÀ2	715	ьys	FEO	GIU	GIU	Met 720

Ala Lys Gln Arg Ser Val Phe Ala Glu Gly Ala Glu Lys Asn Gly Ile 730 725 Asn Ala Glu Leu Ala Met Lys Ile Phe Asp Leu Val Glu Lys Phe Ala 745 Gly Tyr Gly Phe Asn Lys Ser His Ser Ala Ala Tyr Ala Leu Val Ser 760 Tyr Gln Thr Leu Trp Leu Lys Ala His Tyr Pro Ala Glu Phe Met Ala 775 780 Ala Val Met Thr Ala Asp Met Asp Asn Thr Glu Lys Val Val Gly Leu 795 785 790 Val Asp Glu Cys Trp Arg Met Gly Leu Lys Ile Leu Pro Pro Asp Ile 805 810 815 Asn Ser Gly Leu Tyr His Phe His Val Asn Asp Asp Gly Glu Ile Val 825 Tyr Gly Ile Gly Ala Ile Lys Gly Val Gly Glu Gly Pro Ile Glu Ala 840 Ile Ile Glu Ala Arg Asn Lys Gly Gly Tyr Phe Arg Glu Leu Phe Asp 855 860 Leu Cys Ala Arg Thr Asp Thr Lys Lys Leu Asn Arg Arg Val Leu Glu 870 875 Lys Leu Ile Met Ser Gly Ala Phe Asp Arg Leu Gly Pro His Arg Ala 890 Ala Leu Met Asn Ser Leu Gly Asp Ala Leu Lys Ala Ala Asp Gln His 905 910 Ala Lys Ala Glu Ala Ile Gly Gln Ala Asp Met Phe Gly Val Leu Ala 920 925 Glu Glu Pro Glu Gln Ile Glu Gln Ser Tyr Ala Ser Cys Gln Pro Trp 940 935 Pro Glu Gln Val Val Leu Asp Gly Glu Arg Glu Thr Leu Gly Leu Tyr 955 950 Leu Thr Gly His Pro Ile Asn Gln Tyr Leu Lys Glu Ile Glu Arg Tyr 965 970 Val Gly Gly Val Arg Leu Lys Asp Met His Pro Thr Glu Arg Gly Lys 980 985 Val Ile Thr Ala Ala Gly Leu Val Val Ala Ala Arg Val Met Val Thr 995 1000 Lys Arg Gly Asn Arg Ile Gly Ile Cys Thr Leu Asp Asp Arg Ser Gly 1010 1015 1020 Arg Leu Glu Val Met Leu Phe Thr Asp Ala Leu Asp Lys Tyr Gln Gln 1030 1035 Leu Leu Glu Lys Asp Arg Ile Leu Ile Val Ser Gly Gln Val Ser Phe 1050 1045 Asp Asp Phe Ser Gly Gly Leu Lys Met Thr Ala Arg Glu Val Met Asp 1060 1065 1070 Ile Asp Glu Ala Arg Glu Lys Tyr Ala Arg Gly Leu Ala Ile Ser Leu 1080 1085 Thr Asp Arg Gln Ile Asp Asp Gln Leu Leu Asn Arg Leu Arg Gln Ser 1095 1100 1090 Leu Glu Pro His Arg Ser Gly Thr Ile Pro Val His Leu Tyr Tyr Gln 1105 1110 1115 Arg Ala Asp Ala Arg Ala Arg Leu Arg Phe Gly Ala Thr Trp Arg Val 1130 1135 1125 Ser Pro Ser Asp Arg Leu Leu Asn Asp Leu Arg Gly Leu Ile Gly Ser 1140 1145 Glu Gln Val Glu Leu Glu Phe Asp 1160 1155 <210> 402 <211> 239

<212> PRT

<213> Escherichia coli

<400> 402 Met Asn Val Asn Phe Phe Val Thr Cys Ile Gly Asp Ala Leu Lys Ser Arg Met Ala Arg Asp Ser Val Leu Leu Glu Lys Leu Gly Cys Arg Val Asn Phe Pro Glu Lys Gln Gly Cys Cys Gly Gln Pro Ala Ile Asn 40 Ser Gly Tyr Ile Lys Glu Ala Ile Pro Gly Met Lys Asn Leu Ile Ala 55 Ala Leu Glu Asp Asn Asp Asp Pro Ile Ile Ser Pro Ala Gly Ser Cys Thr Tyr Ala Val Lys Ser Tyr Pro Thr Tyr Leu Ala Asp Glu Pro Glu 90 Trp Ala Ser Arg Ala Ala Lys Val Ala Ala Arg Met Gln Asp Leu Thr 105 100 Ser Phe Ile Val Asn Lys Leu Gly Val Val Asp Val Gly Ala Ser Leu 120 125 Gln Gly Arg Ala Val Tyr His Pro Ser Cys Ser Leu Ala Arg Lys Leu 135 Gly Val Lys Asp Glu Pro Leu Thr Leu Leu Lys Asn Val Arg Gly Leu 150 155 Glu Leu Leu Thr Phe Ala Glu Gln Asp Thr Cys Cys Gly Phe Gly Gly 170 165 Thr Phe Ser Val Lys Met Ala Glu Ile Ser Gly Glu Met Val Lys Glu 185 180 Lys Val Ala His Leu Met Glu Val Arg Pro Glu Tyr Leu Ile Gly Ala 200 Asp Val Ser Cys Leu Leu Asn Ile Ser Gly Arg Leu Gln Arg Glu Gly 215 220 Gln Lys Val Lys Val Met His Ile Ala Glu Val Leu Met Ser Arg 230

<210> 403

<211> 475

<212> PRT

<213> Escherichia coli

<400> 403

Met Ser Ile Lys Thr Ser Asn Thr Asp Phe Lys Thr Arg Ile Arg Gln 10 Gln Ile Glu Asp Pro Ile Met Arg Lys Ala Val Ala Asn Ala Gln Gln 20 25 Arg Ile Gly Ala Asn Arg Gln Lys Met Val Asp Glu Leu Gly His Trp 40 Glu Glu Trp Arg Asp Arg Ala Ala Gln Ile Arg Asp His Val Leu Ser 55 60 Asn Leu Asp Ala Tyr Leu Tyr Gln Leu Ser Glu Lys Val Thr Gln Asn 70 75 Gly Gly His Val Tyr Phe Ala Arg Thr Lys Glu Asp Ala Thr Arg Tyr 85 90 Ile Leu Gln Val Ala Gln Arg Lys Asn Ala Arg Lys Val Val Lys Ser 105 100 Lys Ser Met Val Thr Glu Glu Ile Gly Val Asn His Val Leu Gln Asp 120 125 Ala Gly Ile Gln Val Ile Glu Thr Asp Leu Gly Glu Tyr Ile Leu Gln 135 140 Leu Asp Gln Asp Pro Pro Ser His Val Val Val Pro Ala Ile His Lys 155 150

```
Asp Arg His Gln Ile Arg Arg Val Leu His Glu Arg Leu Gly Tyr Glu
               165
                                  170
Gly Pro Glu Thr Pro Glu Ala Met Thr Leu Phe Ile Arg Gln Lys Ile
                               185
           180
Arg Glu Asp Phe Leu Ser Ala Glu Ile Gly Ile Thr Gly Cys Asn Phe
                          200
Ala Val Ala Glu Thr Gly Ser Val Cys Leu Val Thr Asn Glu Gly Asn
                      215
                                          220
Ala Arg Met Cys Thr Thr Leu Pro Lys Thr His Ile Ala Val Met Gly
                  230
                             235
Met Glu Arg Ile Ala Pro Thr Phe Ala Glu Val Asp Val Leu Ile Thr
                     250
Met Leu Ala Arg Ser Ala Val Gly Ala Arg Leu Thr Gly Tyr Asn Thr
                               265
Trp Leu Thr Gly Pro Arg Glu Ala Gly His Val Asp Gly Pro Glu Glu
                                              285
Phe His Leu Val Ile Val Asp Asn Gly Arg Ser Glu Val Leu Ala Ser
                       295
                                          300
Glu Phe Arg Asp Val Leu Arg Cys Ile Arg Cys Gly Ala Cys Met Asn
                                       315
                  310
Thr Cys Pro Ala Tyr Arg His Ile Gly Gly His Gly Tyr Gly Ser Ile
Tyr Pro Gly Pro Ile Gly Ala Val Ile Ser Pro Leu Leu Gly Gly Tyr
                              345
Lys Asp Phe Lys Asp Leu Pro Tyr Ala Cys Ser Leu Cys Thr Ala Cys
               360
Asp Asn Val Cys Pro Val Arg Ile Pro Leu Ser Lys Leu Ile Leu Arg
                       375
                                          380
His Arg Arg Val Met Ala Glu Lys Gly Ile Thr Ala Lys Ala Glu Gln
                                       395
                   390
Arg Ala Ile Lys Met Phe Ala Tyr Ala Asn Ser His Pro Gly Leu Trp
               405
                                   410
Lys Val Gly Met Met Ala Gly Ala His Ala Ala Ser Trp Phe Ile Asn
           420
                              425
Gly Gly Lys Thr Pro Leu Lys Phe Gly Ala Ile Ser Asp Trp Met Glu
                          440
       435
Ala Arg Asp Leu Pro Glu Ala Asp Gly Glu Ser Phe Arg Ser Trp Phe
                      455
Lys Lys His Gln Ala Gln Glu Lys Lys Asn Gly
                  470
<210> 404
<211> 282
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Asn Leu Ala Arg Leu Ala Thr Gly Trp Lys His Ala Ile Phe Leu Lys
                               25
Leu Thr Glu Arg Val Ser Val Val Gly Leu Arg Asn Ile Arg Arg
                           40
Arg Lys Arg Met Asp Asn Arg Gly Glu Phe Leu Asn Asn Val Ala Gln
                       55
                                          60
Ala Leu Gly Arg Pro Leu Arg Leu Glu Pro Gln Ala Glu Asp Ala Pro
                   70
                                       75
Leu Asn Asn Tyr Ala Asn Glu Arg Leu Thr Gln Leu Asn Gln Gln
            . 85
                                   90
Arg Cys Asp Ala Phe Ile Gln Phe Ala Ser Asp Val Met Leu Thr Arg
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110
                            105
Cys Glu Leu Thr Ser Glu Ala Lys Ala Ala Glu Ala Ala Ile Arg Leu
                                 125
               120
Cys Lys Glu Leu Gly Asp Gln Ser Val Val Ile Ser Gly Asp Thr Arg
                    135
Leu Glu Glu Leu Gly Ile Ser Glu Arg Leu Gln Gln Glu Cys Asn Ala
                150
                                    155
Val Val Trp Asp Pro Ala Lys Gly Ala Glu Asn Ile Ser Gln Ala Glu
                                170
Gln Ala Lys Val Gly Val Val Tyr Ala Glu Tyr Gly Leu Thr Glu Ser
                            185
Gly Gly Val Val Leu Phe Ser Ala Ala Glu Arg Gly Arg Ser Leu Ser
                        200
       195
Leu Leu Pro Glu Tyr Ser Leu Phe Ile Leu Arg Lys Ser Thr Ile Leu
                     215
                                      220
 210 ·
Pro Arg Val Ala Gln Leu Ala Glu Lys Leu His Gln Lys Ala Gln Ala
                230
                                   235
Gly Glu Arg Met Pro Ser Cys Ile Asn Ile Ile Ser Gly Pro Ser Ser
                   250
             245
Thr Ala Asp Ile Glu Leu Ile Lys Val Val Gly Val His Gly Pro Val
          260 . 265
Lys Ala Val Tyr Leu Ile Ile Glu Asp Cys
   <210> 405
<211> 390
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<213> Escherichia coli
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Met Ser Glu Ile Ala Met His Val Thr Ala Lys Pro Ser Ser Phe Gln
                                10
Cys Asn Leu Lys Cys Asp Tyr Cys Phe Tyr Leu Glu Lys Glu Ser Gln
                             25
   20
Phe Thr His Glu Lys Trp Met Asp Asp Ser Thr Leu Lys Glu Phe Ile
                      40
Lys Gln Tyr Ile Ala Ala Ser Gly Asn Gln Val Tyr Phe Thr Trp Gln
                     55
                                       60
Gly Gly Glu Pro Thr Leu Ala Gly Leu Asp Phe Phe Arg Lys Val Ile
                                    75
                  70
His Tyr Gln Gln Arg Tyr Ala Gly Gln Lys Arg Ile Phe Asn Ala Leu
                                90
              85
Gln Thr Asn Gly Ile Leu Leu Asn Asn Glu Trp Cys Ala Phe Leu Lys
          100
                            105
Glu His Glu Phe Leu Val Gly Ile Ser Ile Asp Gly Pro Gln Glu Leu
                        120
                                          125
His Asp Arg Tyr Arg Arg Ser Asn Ser Gly Asn Gly Thr Phe Ala Lys
                                       140
                     135
Val Ile Ala Ala Ile Glu Arg Leu Lys Ser Tyr Gln Val Glu Phe Asn
                                    155
                 150
Thr Leu Thr Val Ile Asn Asn Val Asn Val His Tyr Pro Leu Glu Val
             165 .
                                170
                                                   175
Tyr His Phe Leu Lys Ser Ile Gly Ser Lys His Met Gln Phe Ile Glu
                                            190
                             185
          180
Leu Leu Glu Thr Gly Thr Pro Asn Ile Asp Phe Ser Gly His Ser Glu
                         200
Asn Thr Phe Arg Ile Ile Asp Phe Ser Val Pro Pro Thr Ala Tyr Gly
                  215
                                       220
Lys Phe Met Ser Thr Ile Phe Met Gln Trp Val Lys Asn Asp Val Gly
                              . 235
                  230
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Glu Ile Phe Ile Arg Gln Phe Glu Ser Phe Val Ser Arg Phe Leu Gly
                                  250
               245
Asn Gly His Thr Ser Cys Ile Phe Gln Glu Ser Cys Lys Asp Asn Leu
           260
                              265
Val Val Glu Ser Asn Gly Asp Ile Tyr Glu Cys Asp His Phe Val Tyr
                          280
Pro Gln Tyr Lys Ile Gly Asn Ile Asn Lys Ser Glu Leu Lys Thr Met
                     295
Asn Ser Val Gln Leu Thr Ala Gln Lys Lys Arg Ile Pro Ala Lys Cys
                  310 315
Gln Gln Cys Ala Tyr Lys Pro Ile Cys Asn Gly Gly Cys Pro Lys His
            325
                                 330
Arg Ile Thr Lys Val Asn Asn Glu Thr Val Ser Tyr Phe Cys Glu Gly
       340
                              345
Tyr Lys Ile Leu Phe Ser Thr Met Val Pro Tyr Met Asn Ala Met Val
                           360
Glu Leu Ala Lys Asn Arg Val Pro Leu Tyr His Ile Met Asp Val Ala
                                         380
                      375
Lys Gln Met Glu Asn Asn
385
<210> 406
<211> 571
<212> PRT
<213> Escherichia coli
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Met Glu Leu Ser Thr Ile Arg Arg Gly Thr Phe Met Lys Ser Ala Leu
                                  10
Lys Lys Ser Val Val Ser Thr Ser Ile Ser Leu Ile Leu Ala Ser Gly
                              25
Met Ala Ala Phe Ala Ala His Ala Ala Asp Asp Val Lys Leu Lys Ala
                          40
Thr Lys Thr Asn Val Ala Phe Ser Asp Phe Thr Pro Thr Glu Tyr Ser
Thr Lys Gly Lys Pro Asn Ile Ile Val Leu Thr Met Asp Asp Leu Gly
                   70
                           75
Tyr Gly Gln Leu Pro Phe Asp Lys Gly Ser Phe Asp Pro Lys Thr Met
              85
                                  90
Glu Asn Arg Glu Val Val Asp Thr Tyr Lys Ile Gly Ile Asp Lys Ala
                              105
Ile Glu Ala Ala Gln Lys Ser Thr Pro Thr Leu Leu Ser Leu Met Asp
                           120
Glu Gly Val Arg Phe Thr Asn Gly Tyr Val Ala His Gly Val Ser Gly
                                          140
                       135
Pro Ser Arg Ala Ala Ile Met Thr Gly Arg Ala Pro Ala Arg Phe Gly
                                     155
                  150
Val Tyr Ser Asn Thr Asp Ala Gln Asp Gly Ile Pro Leu Thr Glu Thr
                                  170
Phe Leu Pro Glu Leu Phe Gln Asn His Gly Tyr Tyr Thr Ala Ala Val
                              185
Gly Lys Trp His Leu Ser Lys Ile Ser Asn Val Pro Val Pro Glu Asp
        195
                          200
                                             205
Lys Gln Thr Arg Asp Tyr His Asp Asn Phe Thr Thr Phe Ser Ala Glu
                                          220
                      215
Glu Trp Gln Pro Gln Asn Arg Gly Phe Asp Tyr Phe Met Gly Phe His
                                      235
                   230
Ala Ala Gly Thr Ala Tyr Tyr Asn Ser Pro Ser Leu Phe Lys Asn Arg
                                  250
Glu Arg Val Pro Ala Lys Gly Tyr Ile Ser Asp Gln Leu Thr Asp Glu
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265

260

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Ala Ile Gly Val Val Asp Arg Ala Lys Thr Leu Asp Gln Pro Phe Met
                          280
                                            285
Leu Tyr Leu Ala Tyr Asn Ala Pro His Leu Pro Asn Asp Asn Pro Ala
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                      295
Pro Asp Gln Tyr Gln Lys Gln Phe Asn Thr Gly Ser Gln Thr Ala Asp
               310
                                    315
Asn Tyr Tyr Ala Ser Val Tyr Ser Val Asp Gln Gly Val Lys Arg Ile
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              325
Leu Glu Gln Leu Lys Lys Asn Gly Gln Tyr Asp Asn Thr Ile Ile Leu
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Phe Thr Ser Asp Asn Gly Ala Val Ile Asp Gly Pro Leu Pro Leu Asn
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Gly Ala Gln Lys Gly Tyr Lys Ser Gln Thr Tyr Pro Gly Gly Thr His
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                                         380
Thr Pro Met Phe Met Trp Trp Lys Gly Lys Leu Gln Pro Gly Asn Tyr
                                     395
               390
Asp Lys Leu Ile Ser Ala Met Asp Phe Tyr Pro Thr Ala Leu Asp Ala
                                 410
Ala Asp Ile Ser Ile Pro Lys Asp Leu Lys Leu Asp Gly Val Ser Leu
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           420
Leu Pro Trp Leu Gln Asp Lys Lys Gln Gly Glu Pro His Lys Asn Leu
                                             445
       435
                          440
Thr Trp Ile Thr Ser Tyr Ser His Trp Phe Asp Glu Glu Asn Ile Pro
                      455
                                         460
Phe Trp Asp Asn Tyr His Lys Phe Val Arg His Gln Ser Asp Asp Tyr
                                     475
                 470
Pro His Asn Pro Asn Thr Glu Asp Leu Ser Gln Phe Ser Tyr Thr Val
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                                 490
Arg Asn Asn Asp Tyr Ser Leu Val Tyr Thr Val Glu Asn Asn Gln Leu
                              505
Gly Leu Tyr Lys Leu Thr Asp Leu Gln Gln Lys Asp Asn Leu Ala Ala
                          520
Ala Asn Pro Gln Val Val Lys Glu Met Gln Gly Val Val Arg Glu Phe
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Ile Asp Ser Ser Gln Pro Pro Leu Ser Glu Val Asn Gln Glu Lys Phe
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           20
His Ser Lys Thr Met Met Ala Ala Phe Ile Ile Ala Ile Lys Gly Thr
                          40
        35
Ile Lys Gln Ala Val Met Leu Gly Leu Ala Ala Thr Ile Ser His Thr
                       55
Ala Val Val Trp Leu Ile Ala Phe Gly Gly Met Val Ile Ser Lys Arg
                   70
                                     75
Phe Thr Ala Gln Ser Ala Glu Pro Trp Leu Gln Leu Ile Ser Ala Val
                                 90
Ile Ile Ile Ser Thr Ala Phe Trp Met Phe Trp Arg Thr Trp Arg Gly
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            100
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Glu Arg Asn Trp Leu Glu Asn Met His Gly His Asp Tyr Glu His His
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                                             125
His His Asp His Glu His His His Asp His Gly His His His His
                       135 ·
Glu His Gly Glu Tyr Gln Asp Ala His Ala Arg Ala His Ala Asn Asp
                         155
                  150
Ile Lys Arg Arg Phe Asp Gly Arg Glu Val Thr Asn Trp Gln Ile Leu
                                170
              165
Leu Phe Gly Leu Thr Gly Gly Leu Ile Pro Cys Pro Ala Ala Ile Thr
                             185
Val Leu Leu Ile Cys Ile Gln Leu Lys Ala Leu Thr Leu Gly Ala Thr
                  200
Leu Val Val Ser Phe Ser Ile Gly Leu Ala Leu Thr Leu Val Thr Val
           215
                                         220
Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser
                   230
                                   235
Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu
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Met Arg
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Ala Phe Arg Ala Ser Phe His Leu His Phe Leu Arg Asn His Gly Ile
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Thr Asn Lys Ile Ser Leu Val Ser Tyr Ile Val Trp Gln Glu Arg Tyr
                         40
    35
Ala Thr Asp Ile Thr Asp Pro Gln Ser Gly Glu Phe Met Thr Ile Lys
                      55
Asn Lys Met Leu Leu Gly Ala Leu Leu Leu Val Thr Ser Ala Ala Trp
                70 75
Ala Ala Pro Ala Thr Ala Gly Ser Thr Asn Thr Ser Gly Ile Ser Lys
                                90
              85
Tyr Glu Leu Ser Ser Phe Ile Ala Asp Phe Lys His Phe Lys Pro Gly
                             105
Asp Thr Val Pro Glu Met Tyr Arg Thr Asp Glu Tyr Asn Ile Lys Gln
                          120
Trp Gln Leu Arg Asn Leu Pro Ala Pro Asp Ala Gly Thr His Trp Thr
                     135
                                        140
Tyr Met Gly Gly Ala Tyr Val Leu Ile Ser Asp Thr Asp Gly Lys Ile
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                                  155
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Met Ala Phe Val Ser Glu Arg Glu Ile Val Arg Lys Ile Phe Ser Lys
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Lys	Ile	Asp	Phe 20	Thr	Ile	Leu	Ala	Phe 25	Phe	Tyr	Ile	Ser	Ser 30	Ile	Phe
Phe	Leu	Leu 35	Cys	Ser	Gly	Val	Leu 40	Phe	Gln	Tyr	Phe	Thr 45	Ala	Ala	Phe
Thr	Lys 50	Gly	Asn	Cys	Tyr	Glu 55	Cys	Ser	Met	Lys	Leu 60	Asp	Tyr	Ile	Lys
65		_			Leu 70					75					80
				85	Ser				90					95	
			100		Ile			105					110		
		115			Leu		120					125			
	130				Leu	135					140				
-	Leu	Ser	Asn	Ser	Leu	Leu	Phe	His	Leu		Lys	Ile	Lys	His	
145		-1	•	0	150		T1.	D	T 011	155	c~~	ת 1 ת	710	T10	160
				165	Ala				170					175	
			180		Ala			185					190		
		195			Asp		200					205			
	210				Glu	215					220				
225	_				Tyr 230					235					240
_				245	Gly				250					255	
	_		260		Pro			265					270		
_		275			Asn		280					285			
	290				Ile	295					300				
305					Ser 310					315					320
				325	Asp				330					335	
			340		Phe			345					350		
		355			Tyr		360					365			
	370					375					380	_			Lys
	Lys	Cys	Glu	Tyr		Gln	Ile	Ser	Asp		Thr	Asn	Thr	Tyr	Asn
385	7.00	71 a	7.00	т∽	390	Th.~	Cly	Pho	Lou	395	Val	Len	Lue	Pro	400
				405					410					415	Asp
			420		Asn			425					430		
		435	-		Lys		440					445			
_	450					455					460				Ser
465					470					475					Glu 480
Ile	Ile	Ile	Ser	Glu 485	Gly	Ser	Leu	Tyr	Gly 490		Val	Asn	Lys	Ser 495	Lys

Lys Ile Lys Ile Tyr Gly Thr Ala Asp Leu Val Phe Val Asp Asn Lys 500 505 Ile Met Asn Leu Arg Lys Ile Thr Tyr Leu Gln Ser Lys Leu Glu Ile 520 525 Phe Gly Ser Ser Ile Met Asp Ile Leu Lys Tyr Ile Phe Gly Leu Gly 535 Leu Leu Ala Ile Ser Ile Lys Phe Ile His Ser Tyr Phe Lys Asn Asp 550 555 Val Asn Glu Asn Leu Phe Leu 565 <210> 410 <211> 363 <212> PRT <213> Escherichia coli <400> 410 Met Ser Asn Phe Ile Asn Ile His Val Leu Ile Ser His Ser Pro Ser 10 Cys Leu Asn Arg Asp Asp Met Asn Met Gln Lys Asp Ala Ile Phe Gly 25 Gly Lys Arg Arg Val Arg Ile Ser Ser Gln Ser Leu Lys Arg Ala Met 40 45 Arg Lys Ser Gly Tyr Tyr Ala Gln Asn Ile Gly Glu Ser Ser Leu Arg 55 Thr Ile His Leu Ala Gln Leu Arg Asp Val Leu Arg Gln Lys Leu Gly 70 75 Glu Arg Phe Asp Gln Lys Ile Ile Asp Lys Thr Leu Ala Leu Leu Ser 90 85 Gly Lys Ser Val Asp Glu Ala Glu Lys Ile Ser Ala Asp Ala Val Thr 100 105 Pro Trp Val Val Gly Glu Ile Ala Trp Phe Cys Glu Gln Val Ala Lys 120 Ala Glu Ala Asp Asn Leu Asp Asp Lys Lys Leu Leu Lys Val Leu Lys 135 140 Glu Asp Ile Ala Ala Ile Arg Val Asn Leu Gln Gln Gly Val Asp Ile 150 155 Ala Leu Ser Gly Arg Met Ala Thr Ser Gly Met Met Thr Glu Leu Gly 165 170 Lys Val Asp Gly Ala Met Ser Ile Ala His Ala Ile Thr Thr His Gln 185 Val Asp Ser Asp Ile Asp Trp Phe Thr Ala Val Asp Asp Leu Gln Glu 200 Gln Gly Ser Ala His Leu Gly Thr Gln Glu Phe Ser Ser Gly Val Phe 215 220 Tyr Arg Tyr Ala Asn Ile Asn Leu Ala Gln Leu Gln Glu Asn Leu Gly 230 235 Gly Ala Ser Arg Glu Gln Ala Leu Glu Ile Ala Thr His Val Val His 250 245 Met Leu Ala Thr Glu Val Pro Gly Ala Lys Gln Arg Thr Tyr Ala Ala 265 260 Phe Asn Pro Ala Asp Met Val Met Val Asn Phe Ser Asp Met Pro Leu 280 Ser Met Ala Asn Ala Phe Glu Lys Ala Val Lys Ala Lys Asp Gly Phe 295 300 Leu Gln Pro Ser Ile Gln Ala Phe Asn Gln Tyr Trp Asp Arg Val Ala 310 315 Asn Gly Tyr Gly Leu Asn Gly Ala Ala Ala Gln Phe Ser Leu Ser Asp 325 330 335 Val Asp Pro Ile Thr Ala Gln Val Lys Gln Met Pro Thr Leu Glu Gln

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Leu Lys Ser Trp Val Arg Asn Asn Gly Glu Ala
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<400> 411
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His Ser Phe Met Val Arg Leu Glu Ile Thr Gly Glu Val Asp Pro His
                       40
Thr Gly Trp Ile Ile Asp Phe Ala Glu Leu Lys Ala Ala Phe Lys Pro
Thr Tyr Glu Arg Leu Asp His His Tyr Leu Asn Asp Ile Pro Gly Leu
                70
                                75
Glu Asn Pro Thr Ser Glu Val Leu Ala Lys Trp Ile Trp Asp Gln Val
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Lys Pro Val Val Pro Leu Leu Ser Ala Val Met Val Lys Glu Thr Cys
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Thr Ala Gly Cys Ile Tyr Arg Gly Glu
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<211> 433
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Ile Ile Ile Gly Ala Gly Ile Ala Gly Thr Ala Cys Ala Leu Arg
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Cys Ala Arg Ala Gly Leu Ser Val Leu Leu Leu Glu Arg Ala Glu Ile
                  40
Pro Gly Ser Lys Asn Leu Ser Gly Gly Arg Leu Tyr Thr His Ala Leu
                                        60
                     55
Ala Glu Leu Leu Pro Gln Phe His Leu Thr Ala Pro Leu Glu Arg Arg
                          75
                  70
Ile Thr His Glu Ser Leu Ser Leu Leu Thr Pro Asp Gly Val Thr Thr
Phe Ser Ser Leu Gln Pro Gly Gly Glu Ser Trp Ser Val Leu Arg Ala
                             105
          100
Arg Phe Asp Pro Trp Leu Val Ala Glu Ala Glu Lys Glu Gly Val Glu
                         120
                                            125
Cys Ile Pro Gly Ala Thr Val Asp Ala Leu Tyr Glu Glu Asn Gly Arg
                                       140
                     135
Val Cys Gly Val Ile Cys Gly Asp Asp Ile Leu Arg Ala Arg Tyr Val
                                    155
                 150
Val Leu Ala Glu Gly Ala Asn Ser Val Leu Ala Glu Arg His Gly Leu
                                                    175
                                170
              165
Val Thr Arg Pro Ala Gly Glu Ala Met Ala Leu Gly Ile Lys Glu Val
                              185
Leu Ser Leu Glu Thr Ser Ala Ile Glu Glu Arg Phe His Leu Glu Asn
               200
Asn Glu Gly Ala Ala Leu Leu Phe Ser Gly Arg Ile Cys Asp Asp Leu
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215
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Pro Gly Gly Ala Phe Leu Tyr Thr Asn Gln Gln Thr Leu Ser Leu Gly
                   230
                                     235
Ile Val Cys Pro Leu Ser Ser Leu Thr Gln Ser Arg Val Pro Ala Ser
                                 250
               245
Glu Leu Leu Thr Arg Phe Lys Ala His Pro Ala Val Arg Pro Leu Ile
          260
                              265
Lys Asn Thr Glu Ser Leu Glu Tyr Gly Ala His Leu Val Pro Glu Gly
                         280
Gly Leu His Ser Met Pro Val Gln Tyr Ala Gly Asn Gly Trp Leu Leu
                      295
                                         300
Val Gly Asp Ala Leu Arg Ser Cys Val Asn Thr Gly Ile Ser Val Arg
                  310
                            315
Gly Met Asp Met Ala Leu Thr Gly Ala Gln Ala Ala Gln Thr Leu
            325
                                  330
Ile Ser Ala Cys Gln His Arg Glu Pro Gln Asn Leu Phe Pro Leu Tyr
                               345
           340
His His Asn Val Glu Arg Ser Leu Leu Trp Asp Val Leu Gln Arg Tyr
                          360
                                              365
Gln His Val Pro Ala Leu Leu Gln Arg Pro Gly Trp Tyr Arg Thr Trp
                      375
                                          380
Pro Ala Leu Met Gln Asp Ile Ser Arg Asp Leu Trp Asp Gln Gly Asp
                   390
                                     395
Lys Pro Val Pro Pro Leu Arg Gln Leu Phe Trp His His Leu Arg Arg
              405
                                 410
His Gly Leu Trp His Leu Ala Gly Asp Val Ile Arg Ser Leu Arg Cys
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Leu
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Arg Asn Leu Trp Arg Val Ala Asp Ala Pro His Ile Val Pro Ala Asp
                               25
Ser Val Glu Arg Gln Thr Ala Glu Arg Leu Ile Asn Ala Cys Pro Ala
                          40
Gly Leu Phe Ser Leu Thr Pro Glu Gly Asn Leu Arg Ile Asp Tyr. Arg
Ser Cys Leu Glu Cys Gly Thr Cys Arg Leu Leu Cys Asp Glu Ser Thr
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                                    75
Leu Gln Gln Trp Arg Tyr Pro Pro Ser Gly Phe Gly Ile Thr Tyr Arg
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Phe Gly
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Met Pro Leu Leu His Leu Leu Arg Gln Asn Pro Val Ile Ala Ala Val
1 5 10 15
Lys Asp Asn Ala Ser Leu Gln Leu Ala Ile Asp Ser Glu Cys Gln Phe

25

20

30

```
Ile Ser Val Leu Tyr Gly Asn Ile Cys Thr Ile Ser Asn Ile Val Lys
                                45
                 40
Lys Ile Lys Asn Ala Gly Lys Tyr Ala Phe Ile His Val Asp Leu Leu
                    55
Glu Gly Ala Ser Asn Lys Glu Val Val Ile Gln Phe Leu Lys Leu Val
               70
Thr Glu Ala Asp Gly Ile Ile Ser Thr Lys Ala Ser Met Leu Lys Ala
             85
                     90
Ala Arg Ala Glu Gly Phe Phe Cys Ile His Arg Leu Phe Ile Val Asp
                          105
          100
Ser Ile Ser Phe His Asn Ile Asp Lys Gln Val Ala Gln Ser Asn Pro
                       120
       115
Asp Cys Ile Glu Ile Leu Pro Gly Cys Met Pro Lys Val Leu Gly Trp
                    135
                             140
Val Thr Glu Lys Ile Arg Gln Pro Leu Ile Ala Gly Gly Leu Val Cys
                      155
        150
Asp Glu Glu Asp Ala Arg Asn Ala Ile Asn Ala Gly Val Val Ala Leu
            165 170 . . . 175
Ser Thr Thr Asn Thr Gly Val Trp Thr Leu Ala Lys Lys Leu Leu
         180 185
<210> 415
                 . :
<211> 134
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<213> Escherichia coli
<400> 415
Met Phe Met Thr Trp Glu Tyr Ala Leu Ile Gly Leu Val Val Gly Ile
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Ile Ile Gly Ala Val Ala Met Arg Phe Gly Asn Arg Lys Leu Arg Gln
                           25
   20
Gln Gln Ala Leu Gln Tyr Glu Leu Glu Lys Asn Lys Ala Glu Leu Asp
                       40
Glu Tyr Arg Glu Glu Leu Val Ser His Phe Ala Arg Ser Ala Glu Leu
                     55
Leu Asp Thr Met Ala His Asp Tyr Arg Gln Leu Tyr Gln His Met Ala
                 70
                                   75
Lys Ser Ser Ser Leu Leu Pro Glu Leu Ser Ala Glu Ala Asn Pro
                               90
             85
Phe Arg Asn Arg Leu Ala Glu Ser Glu Ala Ser Asn Asp Gln Ala Pro
                           105
         100
Val Gln Met Pro Arg Asp Tyr Ser Glu Gly Ala Ser Gly Leu Leu Arg
Thr Gly Ala Lys Arg Asp
  130
<210> 416
<211> 455
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Met Lys Lys Gln Thr Gln Leu Leu Ser Ala Leu Ala Leu Ser Val Gly
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Leu Thr Leu Ser Ala Ser Phe Gln Ala Val Ala Ser Ile Pro Gly Gln
                           25
Val Ala Asp Gln Ala Pro Leu Pro Ser Leu Ala Pro Met Leu Glu Lys
                        40
Val Leu Pro Ala Val Val Ser Val Arg Val Glu Gly Thr Ala Ser Gln
```

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55
Gly Gln Lys Ile Pro Glu Glu Phe Lys Lys Phe Phe Gly Asp Asp Leu
                 70
                                    75
Pro Asp Gln Pro Ala Gln Pro Phe Glu Gly Leu Gly Ser Gly Val Ile
                               90
             85
Ile Asn Ala Ser Lys Gly Tyr Val Leu Thr Asn Asn His Val Ile Asn
          100
                            105
Gln Ala Gln Lys Ile Ser Ile Gln Leu Asn Asp Gly Arg Glu Phe Asp
                 120
Ala Lys Leu Ile Gly Ser Asp Asp Gln Ser Asp Ile Ala Leu Leu Gln
           135
                                      140
Ile Gln Asn Pro Ser Lys Leu Thr Gln Ile Ala Ile Ala Asp Ser Asp
       150
                                   155
Lys Leu Arg Val Gly Asp Phe Ala Val Ala Val Gly Asn Pro Phe Gly
                                170
             165
Leu Gly Gln Thr Ala Thr Ser Gly Ile Val Ser Ala Leu Gly Arg Ser
                             185
Gly Leu Asn Leu Glu Gly Leu Glu Asn Phe Ile Gln Thr Asp Ala Ser
                         200
Ile Asn Arg Gly Asn Ser Gly Gly Ala Leu Leu Asn Leu Asn Gly Glu
                    215
                                       220
Leu Ile Gly Ile Asn Thr Ala Ile Leu Ala Pro Gly Gly Ser Val
                  230
                                   235
Gly Ile Gly Phe Ala Ile Pro Ser Asn Met Ala Arg Thr Leu Ala Gln
            245
                               250
Gln Leu Ile Asp Phe Gly Glu Ile Lys Arg Gly Leu Leu Gly Ile Lys
                            265
          260
Gly Thr Glu Met Ser Ala Asp Ile Ala Lys Ala Phe Asn Leu Asp Val
                        280
Gln Arg Gly Ala Phe Val Ser Glu Val Leu Pro Gly Ser Gly Ser Ala
           295 300
Lys Ala Gly Val Lys Ala Gly Asp Ile Ile Thr Ser Leu Asn Gly Lys
                 310
                                   315
Pro Leu Asn Ser Phe Ala Glu Leu Arg Ser Arg Ile Ala Thr Thr Glu
             325
Pro Gly Thr Lys Val Lys Leu Gly Leu Leu Arg Asn Gly Lys Pro Leu
                345 350
Glu Val Glu Val Thr Leu Asp Thr Ser Thr Ser Ser Ser Ala Ser Ala
       355 360 365
Glu Met Ile Thr Pro Ala Leu Glu Gly Ala Thr Leu Ser Asp Gly Gln
                     375
Leu Lys Asp Gly Gly Lys Gly Ile Lys Ile Asp Glu Val Val Lys Gly
                  390
                                    395
Ser Pro Ala Ala Gln Ala Gly Leu Gln Lys Asp Asp Val Ile Ile Gly
              405
                                410
Val Asn Arg Asp Arg Val Asn Ser Ile Ala Glu Met Arg Lys Val Leu
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Ala Ala Lys Pro Ala Ile Ile Ala Leu Gln Ile Val Arg Gly Asn Glu
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Ser Ile Tyr Leu Leu Met Arg
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                             25
Ser Thr Pro Gln Phe Asp Ser Thr Asp Glu Thr Pro Ala Ser Tyr Asn
                          40
Leu Ala Val Arg Arg Ala Ala Pro Ala Val Val Asn Val Tyr Asn Arg
                   · 55
Gly Leu Asn Thr Asn Ser His Asn Gln Leu Glu Ile Arg Thr Leu Gly
Ser Gly Val Ile Met Asp Gln Arg Gly Tyr Ile Ile Thr Asn Lys His
                                  90
Val Ile Asn Asp Ala Asp Gln Ile Ile Val Ala Leu Gln Asp Gly Arg
                             105
           100
Val Phe Glu Ala Leu Leu Val Gly Ser Asp Ser Leu Thr Asp Leu Ala
                                            125
                          120
Val Leu Lys Ile Asn Ala Thr Gly Gly Leu Pro Thr Ile Pro Ile Asn
                                        140
                      135
Ala Arg Arg Val Pro His Ile Gly Asp Val Val Leu Ala Ile Gly Asn
                                    155
                  150
Pro Tyr Asn Leu Gly Gln Thr Ile Thr Gln Gly Ile Ile Ser Ala Thr
                                  170
               165
Gly Arg Ile Gly Leu Asn Pro Thr Gly Arg Gln Asn Phe Leu Gln Thr
          180
                             185
                                              190
Asp Ala Ser Ile Asn His Gly Asn Ser Gly Gly Ala Leu Val Asn Ser
                           200 205
Leu Gly Glu Leu Met Gly Ile Asn Thr Leu Ser Phe Asp Lys Ser Asn
                                         220
                      215
Asp Gly Glu Thr Pro Glu Gly Ile Gly Phe Ala Ile Pro Phe Gln Leu
                                     235
                  230
Ala Thr Lys Ile Met Asp Lys Leu Ile Arg Asp Gly Arg Val Ile Arg
              245
                                  250
Gly Tyr Ile Gly Ile Gly Gly Arg Glu Ile Ala Pro Leu His Ala Gln
                             265
Gly Gly Gly Ile Asp Gln Leu Gln Gly Ile Val Val Asn Glu Val Ser
                280
Pro Asp Gly Pro Ala Ala Asn Ala Gly Ile Gln Val Asn Asp Leu Ile
            295
                                          300
Ile Ser Val Asp Asn Lys Pro Ala Ile Ser Ala Leu Glu Thr Met Asp
                                      315
                  310
Gln Val Ala Glu Ile Arg Pro Gly Ser Val Ile Pro Val Val Met
                                 330
               325
Arg Asp Asp Lys Gln Leu Thr Leu Gln Val Thr Ile Gln Glu Tyr Pro
                               345
Ala Thr Asn
       355
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 Met Ala Arg Ile Ala Gly Ile Asn Ile Pro Asp His Lys His Ala Val
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 Ile Ala Leu Thr Ser Ile Tyr Gly Val Gly Lys Thr Arg Ser Lys Ala
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 Ile Leu Ala Ala Gly Ile Ala Glu Asp Val Lys Ile Ser Glu Leu
                           40
 Ser Glu Gly Gln Ile Asp Thr Leu Arg Asp Glu Val Ala Lys Phe Val
                       55
 Val Glu Gly Asp Leu Arg Arg Glu Ile Ser Met Ser Ile Lys Arg Leu
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70 75 Met Asp Leu Gly Cys Tyr Arg Gly Leu Arg His Arg Arg Gly Leu Pro 90 Val Arg Gly Gln Arg Thr Lys Thr Asn Ala Arg Thr Arg Lys Gly Pro 105 100 Arg Lys Pro Ile Lys Lys 115 <210> 419 <211> 129 <212> PRT <213> Escherichia coli <400> 419 Met Ala Lys Ala Pro Ile Arg Ala Arg Lys Arg Val Arg Lys Gln Val 10 Ser Asp Gly Val Ala His Ile His Ala Ser Phe Asn Asn Thr Ile Val 20 25 Thr Ile Thr Asp Arg Gln Gly Asn Ala Leu Gly Trp Ala Thr Ala Gly Gly Ser Gly Phe Arg Gly Ser Arg Lys Ser Thr Pro Phe Ala Ala Gln 55 Val Ala Ala Glu Arg Cys Ala Asp Ala Val Lys Glu Tyr Gly Ile Lys 70 75 Asn Leu Glu Val Met Val Lys Gly Pro Gly Pro Gly Arg Glu Ser Thr 90 85 Ile Arg Ala Leu Asn Ala Ala Gly Phe Arg Ile Thr Asn Ile Thr Asp 100 105 Val Thr Pro Ile Pro His Asn Gly Cys Arg Pro Pro Lys Lys Arg Arg 120 Val <210> 420 <211> 206 <212> PRT <213> Escherichia coli <400> 420 Met Ala Arg Tyr Leu Gly Pro Lys Leu Lys Leu Ser Arg Arg Glu Gly 10 5 Thr Asp Leu Phe Leu Lys Ser Gly Val Arg Ala Ile Asp Thr Lys Cys 25′ Lys Ile Glu Gln Ala Pro Gly Gln His Gly Ala Arg Lys Pro Arg Leu 40 Ser Asp Tyr Gly Val Gln Leu Arg Glu Lys Gln Lys Val Arg Arg Ile 55 Tyr Gly Val Leu Glu Arg Gln Phe Arg Asn Tyr Tyr Lys Glu Ala Ala 75 Arg Leu Lys Gly Asn Thr Gly Glu Asn Leu Leu Ala Leu Leu Glu Gly 90 Arg Leu Asp Asn Val Val Tyr Arg Met Gly Phe Gly Ala Thr Arg Ala 100 105 110 Glu Ala Arg Gln Leu Val Ser His Lys Ala Ile Met Val Asn Gly Arg 125 120 Val Val Asn Ile Ala Ser Tyr Gln Val Ser Pro Asn Asp Val Val Ser 135 140 Ile Arg Glu Lys Ala Lys Lys Gln Ser Arg Val Lys Ala Ala Leu Glu 155 150 Leu Ala Glu Gln Arg Glu Lys Pro Thr Trp Leu Glu Val Asp Ala Gly

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170
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Lys Met Glu Gly Thr Phe Lys Arg Lys Pro Glu Arg Ser Asp Leu Ser
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                  185
Ala Asp Ile Asn Glu His Leu Ile Val Glu Leu Tyr Ser Lys
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Glu Gln Val Ser Ser Thr His Ala Lys Val Thr Leu Glu Pro Leu Glu
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Arg Gly Phe Gly His Thr Leu Gly Asn Ala Leu Arg Arg Ile Leu Leu
                         40
Ser Ser Met Pro Gly Cys Ala Val Thr Glu Val Glu Ile Asp Gly Val
                     55
Leu His Glu Tyr Ser Thr Lys Glu Gly Val Gln Glu Asp Ile Leu Glu
Ile Leu Leu Asn Leu Lys Gly Leu Ala Val Arg Val Gln Gly Lys Asp
                                90
Glu Val Ile Leu Thr Leu Asn Lys Ser Gly Ile Gly Pro Val Thr Ala
                            105
          100
Ala Asp Ile Thr His Asp Gly Asp Val Glu Ile Val Lys Pro Gln His
                       120
Val Ile Cys His Leu Thr Asp Glu Asn Ala Ser Ile Ser Met Arg Ile
                     135
                                140
Lys Val Gln Arg Gly Arg Gly Tyr Val Pro Ala Ser Thr Arg Ile His
                 150
                            155
Ser Glu Glu Asp Glu Arg Pro Ile Gly Arg Leu Leu Val Asp Ala Cys
                                170
             165
Tyr Ser Pro Val Glu Arg Ile Ala Tyr Asn Val Glu Ala Ala Arg Val
        180 . 185
Glu Gln Arg Thr Asp Leu Asp Lys Leu Val Ile Glu Met Glu Thr Asn
                         200
                                            205
      195
Gly Thr Ile Asp Pro Glu Glu Ala Ile Arg Arg Ala Ala Thr Ile Leu
                                        220
                      215
Ala Glu Gln Leu Glu Ala Phe Val Asp Leu Arg Asp Val Arg Gln Pro
                                   · 235
                 230
Glu Val Lys Glu Glu Lys Pro Glu Phe Asp Pro Ile Leu Leu Arg Pro
              245
                                250
Val Asp Asp Leu Glu Leu Thr Val Arg Ser Ala Asn Cys Leu Lys Ala
                            265
Glu Ala Ile His Tyr Ile Gly Asp Leu Val Gln Arg Thr Glu Val Glu
                                           285
      275 . 280
Leu Leu Lys Thr Pro Asn Leu Gly Lys Lys Ser Leu Thr Glu Ile Lys
  290 295
                                        300
Asp. Val Leu Ala Ser Arg Gly Leu Ser Leu Gly Met Arg Leu Glu Asn
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Trp Pro Pro Ala Ser Ile Ala Asp Glu
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Arg Gln Ala Met Phe Arg Asn Met Ala Gly Ser Leu Val Arg His Glu
Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val
                           40
Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg
                      55
Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe
                  70
Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg
                                  90
Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr
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          100
Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu
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<211> 46
<212> PRT
<213> Escherichia coli
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Met Lys Arg Thr Phe Gln Pro Ser Val Leu Lys Arg Asn Arg Ser His
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Gly Phe Arg Ala Arg Met Ala Thr Lys Asn Gly Arg Gln Val Leu Ala
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Arg Arg Arg Ala Lys Gly Arg Ala Arg Leu Thr Val Ser Lys
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<211> 119
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Gln Phe Thr Phe Val Phe Gln Gln Pro Gln Arg Ala Gly Thr Pro Gln
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Ile Thr Ile Leu Gly Arg Leu Asn Ser Leu Gly His Pro Arg Ile Gly
Leu Thr Val Ala Lys Lys Asn Val Arg Arg Ala His Glu Arg Asn Arg
Ile Lys Arg Leu Thr Arg Glu Ser Phe Arg Leu Arg Gln His Glu Leu
                                       75
Pro Ala Met Asp Phe Val Val Val Ala Lys Lys Gly Val Ala Asp Leu
                                   90
Asp Asn Arg Ala Leu Ser Glu Ala Leu Glu Lys Leu Trp Arg Arg His
Cys Arg Leu Ala Arg Gly Ser
<210> 425
<211> 591
<212> PRT
<213> Escherichia coli
<400> 425
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Met Ile Glu Lys Leu Arg Asn Ile Ala Ile Ile Ala His Val Asp His 10 Gly Lys Thr Thr Leu Val Asp Lys Leu Leu Gln Gln Ser Gly Thr Phe 25 Asp Ser Arg Ala Glu Thr Gln Glu Arg Val Met Asp Ser Asn Asp Leu 40 Glu Lys Glu Arg Gly Ile Thr Ile Leu Ala Lys Asn Thr Ala Ile Lys Trp Asn Asp Tyr Arg Ile Asn Ile Val Asp Thr Pro Gly His Ala Asp 70 75 Phe Gly Gly Glu Val Glu Arg Val Met Ser Met Val Asp Ser Val Leu 90 Leu Val Val Asp Ala Phe Asp Gly Pro Met Pro Gln Thr Arg Phe Val 105 . 110 100 Thr Lys Lys Ala Phe Ala Tyr Gly Leu Lys Pro Ile Val Val Ile Asn 120 115 Lys Val Asp Arg Pro Gly Ala Arg Pro Asp Trp Val Val Asp Gln Val 135 140 Phe Asp Leu Phe Val Asn Leu Asp Ala Thr Asp Glu Gln Leu Asp Phe 155 150 Pro Ile Val Tyr Ala Ser Ala Leu Asn Gly Ile Ala Gly Leu Asp His 165 170 Glu Asp Met Ala Glu Asp Met Thr Pro Leu Tyr Gln Ala Ile Val Asp 185 180 His Val Pro Ala Pro Asp Val Asp Leu Asp Gly Pro Phe Gln Met Gln 200 Ile Ser Gln Leu Asp Tyr Asn Ser Tyr Val Gly Val Ile Gly Ile Gly 215 220 Arg Ile Lys Arg Gly Lys Val Lys Pro Asn Gln Gln Val Thr Ile Ile 230 235 Asp Ser Glu Gly Lys Thr Arg Asn Ala Lys Val Gly Lys Val Leu Gly 250 245 His Leu Gly Leu Glu Arg Ile Glu Thr Asp Leu Ala Glu Ala Gly Asp 265 Ile Val Ala Ile Thr Gly Leu Gly Glu Leu Asn Ile Ser Asp Thr Val 280 Cys Asp Thr Gln Asn Val Glu Ala Leu Pro Ala Leu Ser Val Asp Glu 295 · Pro Thr Val Ser Met Phe Phe Cys Val Asn Thr Ser Pro Phe Cys Gly 315 310 Lys Glu Gly Lys Phe Val Thr Ser Arg Gln Ile Leu Asp Arg Leu Asn 330 325 Lys Glu Leu Val His Asn Val Ala Leu Arg Val Glu Glu Thr Glu Asp 345 340 Ala Asp Ala Phe Arg Val Ser Gly Arg Gly Glu Leu His Leu Ser Val 360 Leu Ile Glu Asn Met Arg Arg Glu Gly Phe Glu Leu Ala Val Ser Arg 375 380 Pro Lys Val Ile Phe Arg Glu Ile Asp Gly Arg Lys Gln Glu Pro Tyr 395 390 Glu Asn Val Thr Leu Asp Val Glu Glu Gln His Gln Gly Ser Val Met 405 410 Gln Ala Leu Gly Glu Arg Lys Gly Asp Leu Lys Asn Met Asn Pro Asp 425 420 Gly Lys Gly Arg Val Arg Leu Asp Tyr Val Ile Pro Ser Arg Gly Leu 440 Ile Gly Phe Arg Ser Glu Phe Met Thr Met Thr Ser Gly Thr Gly Leu 460 455 Leu Tyr Ser Thr Phe Ser His Tyr Asp Asp Val Arg Pro Gly Glu Val 475 470

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Gly Gln Arg Gln Asn Gly Val Leu Ile Ser Asn Gly Gln Gly Lys Ala
                                  490
               485
Val Ala Phe Ala Leu Phe Gly Leu Gln Asp Arg Gly Lys Leu Phe Leu
                               505
Gly His Gly Ala Glu Val Tyr Glu Gly Gln Ile Ile Gly Ile His Ser
                          520
Arg Ser Asn Asp Leu Thr Val Asn Cys Leu Thr Gly Lys Lys Leu Thr
         535
                                         540
Asn Met Arg Ala Ser Gly Thr Asp Glu Ala Val Val Leu Val Pro Pro
                                     555
                550
Ile Arg Met Thr Leu Glu Gln Ala Leu Glu Phe Ile Asp Asp Asp Glu
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Leu Val Glu Val Thr Pro Thr Ser Ile Arg Ile Arg Lys Arg His
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<212> PRT
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Trp Val Gly Asn Ala Val Glu Arg Leu Ala Asp Ala Leu Ser Gln Gln
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Asn Val Thr Val Ile Lys Ser Thr Ser Phe Asp Asp Gly Phe Ala Ile
                          40
Leu Ser Ser Asn Glu Ala Ile Asp Cys Leu Met Phe Ser Tyr Gln Met
                       55
Glu His Pro Asp Glu His Gln Asn Val Arg Gln Leu Ile Gly Lys Leu
                   70
His Glu Arg Gln Gln Asn Val Pro Val Phe Leu Leu Gly Asp Arg Glu
                                  90
               85
Lys Ala Leu Ala Ala Met Asp Arg Asp Leu Leu Glu Leu Val Asp Glu
                              105
          100
Phe Ala Trp Ile Leu Glu Asp Thr Ala Asp Phe Ile Ala Gly Arg Ala
                          120
Val Ala Ala Met Thr Arg Tyr Arg Gln Gln Leu Leu Pro Pro Leu Phe
                      135
                               140
Ser Ala Leu Met Lys Tyr Ser Asp Ile His Glu Tyr Ser Trp Ala Ala
                 150
                                      155
Pro Gly His Gln Gly Gly Val Gly Phe Thr Lys Thr Pro Ala Gly Arg
                                   170
Phe Tyr His Asp Tyr Tyr Gly Glu Asn Leu Phe Arg Thr Asp Met Gly
                               185
                                                  190
           180
Ile Glu Arg Thr Ser Leu Gly Ser Leu Leu Asp His Thr Gly Ala Phe
                           200
Gly Glu Ser Glu Lys Tyr Ala Ala Arg Val Phe Gly Ala Asp Arg Ser
                                          220
                       215
Trp Ser Val Val Val Gly Thr Ser Gly Ser Asn Arg Thr Ile Met Gln
                                       235
                   230
Ala Cys Met Thr Asp Asn Asp Val Val Val Asp Arg Asn Cys His
               245
                                  250
Lys Ser Ile Glu Gln Gly Leu Met Leu Thr Gly Ala Lys Pro Val Tyr
                              265
Met Val Pro Ser Arg Asn Arg Tyr Gly Ile Ile Gly Pro Ile Tyr Pro
                           280
Gln Glu Met Gln Pro Glu Thr Leu Gln Lys Lys Ile Ser Glu Ser Pro
                       295
Leu Thr Lys Asp Lys Ala Gly Gln Lys Pro Ser Tyr Cys Val Val Thr
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305					310					315					320
Asn	Cys	Thr	Tyr	Asp 325	Gly	Val	Cys	Tyr	Asn 330	Ala	Lys	Glu	Ala	Gln 335	Asp
			Lys 340					345					350		
_	•	355	Arg				360					365			
_	370		Gly			375					380				
385		_	Leu		390					395					400
-			Arg	405					410					415	
			Ala 420					425					430		
		435	Val				440					445			
	450		Ile			455					460				
465	_	_	Glu		470					475					480
		•	Val	485					490			•		495	
			Pro 500					505					510	•	
		515	Gly				520					525			
-	530		Leu			535					540				
545		-	Gly		550					555					560
		_	Leu	565					570					575	
			Met 580					585					590		
_		595	Val				600					605			
	610		Leu			615					620				
Asp 625	Thr	Tyr	Ala	Asn	Met 630	GIY	ite	HIS	Asp	635	GLY	Asp	Thr	Met	640
			Lys	645					650					655	
			Pro 660					665					670		
		675					680					685			Gly
_	690					695					700	•			Met
705			_		710					715					Ser 720
_		_		725					730					735	Glu
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Cys	Val	Lys 755	Ala												
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<212> PRT <213> Escherichia coli <400> 427 Met Arg Ile Cys Ser Asp Gln Pro Cys Ile Val Leu Leu Thr Glu Lys 10 Asp Val Trp Ile Arg Val Asn Gly Lys Glu Pro Ile Ser Leu Lys Ala Asn His Met Ala Leu Leu Asn Cys Glu Asn Asn Ile Ile Asp Val Ser 40 Ser Leu Asn Asn Thr Leu Val Ala His Ile Ser His Asp Ile Ile Lys 55 Asp Tyr Leu Arg Phe Leu Asn Lys Asp Leu Ser Gln Ile Pro Val Trp Gln Arg Ser Ala Thr Pro Ile Leu Thr Leu Pro Cys Leu Thr Pro Asp 90 Val Phe Arg Val Ala Ala Gln His Ser Met Met Pro Ala Glu Thr Glu 100 105 Ser Glu Lys Glu Arg Thr Arg Ala Leu Leu Phe Thr Val Leu Ser Arg 115 120 Phe Leu Asp Ser Lys Lys Phe Val Ser Leu Met Met Tyr Met Leu Arg 135 Asn Cys Val Ser Asp Ser Val Tyr Gln Ile Ile Glu Ser Asp Ile His 150 155 Lys Asp Trp Asn Leu Ser Met Val Ala Ser Cys Leu Cys Leu Ser Pro 165 170 175 Ser Leu Leu Lys Lys Lys Leu Lys Ser Glu Asn Thr Ser Tyr Ser Gln 185 180 Ile Ile Thr Thr Cys Arg Met Arg Tyr Ala Val Asn Glu Leu Met Met 200 205 Asp Gly Lys Asn Ile Ser Gln Val Ser Gln Ser Cys Gly Tyr Asn Ser 210 215 220 Thr Ser Tyr Phe Ile Ser Val Phe Lys Asp Phe Tyr Gly Met Thr Pro 230 Leu His Tyr Val Ser Gln His Arg Glu Arg Thr Val Ala <210> 428 <211> 425 <212> PRT <213> Escherichia coli <400> 428 Met Leu Arg Leu Pro Asn Ile Tyr Phe Lys Gly Tyr Ile Arg Ile Thr 10 Gln Glu Thr Asn Met Ala Thr Ala Trp Tyr Lys Gln Val Asn Pro Pro 25 Gln Arg Lys Ala Leu Phe Ser Ala Trp Leu Gly Tyr Val Phe Asp Gly 40 Phe Asp Phe Met Met Ile Phe Tyr Ile Leu His Ile Ile Lys Ala Asp 55 60 Leu Gly Ile Thr Asp Ile Gln Ala Thr Leu Ile Gly Thr Val Ala Phe 70 75 Ile Ala Arg Pro Ile Gly Gly Gly Phe Phe Gly Ala Met Ala Asp Lys 90 Tyr Gly Arg Lys Pro Met Met Trp Ala Ile Phe Ile Tyr Ser Val 105 Gly Thr Gly Leu Ser Gly Ile Ala Thr Asn Leu Tyr Met Leu Ala Val 120

Cys Arg Phe Ile Val Gly Leu Gly Met Ser Gly Glu Tyr Ala Cys Ala

135

140

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Ser Thr Tyr Ala Val Glu Ser Trp Pro Lys Asn Leu Gln Ser Lys Ala
                                    155
          150
Ser Ala Phe Leu Val Ser Gly Phe Ser Val Gly Asn Ile Ile Ala Ala
                                170
             165
Gln Ile Ile Pro Gln Phe Ala Glu Val Tyr Gly Trp Arg Asn Ser Phe
                            185
Phe Ile Gly Leu Leu Pro Val Leu Leu Val Leu Trp Ile Arg Lys Ser
               200
Ala Pro Glu Ser Gln Glu Trp Ile Glu Asp Lys Tyr Lys Asp Lys Ser
                    215
                                       220
Thr Phe Leu Ser Val Phe Arg Lys Pro His Leu Ser Ile Ser Met Ile
                  230
                                     235
Val Phe Leu Val Cys Phe Cys Leu Phe Gly Ala Asn Trp Pro Ile Asn
                                250
              245
Gly Leu Leu Pro Ser Tyr Leu Ala Asp Asn Gly Val Asn Thr Val Val
                             265
           260
Ile Ser Thr Leu Met Thr Ile Ala Gly Leu Gly Thr Leu Thr Gly Thr
                         280
Ile Phe Phe Gly Phe Val Gly Asp Lys Ile Gly Val Lys Lys Ala Phe
            295
                                       300
Val Val Gly Leu Ile Thr Ser Phe Ile Phe Leu Cys Pro Leu Phe Phe
          310 315
Ile Ser Val Lys Asn Ser Ser Leu Ile Gly Leu Cys Leu Phe Gly Leu
             325
                                 330
                                                    335
Met Phe Thr Asn Leu Gly Ile Ala Gly Leu Val Pro Lys Phe Ile Tyr
Asp Tyr Phe Pro Thr Lys Leu Arg Gly Leu Gly Thr Gly Leu Ile Tyr
                         360
                                           365
Asn Leu Gly Ala Thr Gly Gly Met Ala Ala Pro Val Leu Ala Thr Tyr
                               380
                     375
Ile Ser Gly Tyr Tyr Gly Leu Gly Val Ser Leu Phe Ile Val Thr Val
                390
                                    395
Ala Phe Ser Ala Leu Leu Ile Leu Leu Val Gly Phe Asp Ile Pro Gly
             405
Lys Ile Tyr Lys Leu Ser Val Ala Lys
<210> 429
<211> 377
<212> PRT
<213> Escherichia coli
<400> 429
Met Ile Gly Gly Phe Met Ile Asn Tyr Gly Val Val Gly Val Gly Tyr
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Phe Gly Ala Glu Leu Ala Arg Phe Met Asn Met His Asp Asn Ala Lys
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                             25
Ile Thr Cys Val Tyr Asp Pro Glu Asn Gly Glu Asn Ile Ala Arg Glu
               40
Leu Gln Cys Ile Asn Met Ser Ser Leu Asp Ala Leu Val Ser Ser Lys
                     · 55
                                        60
Leu Val Asp Cys Val Ile Val Ala Thr Pro Asn Tyr Leu His Lys Glu
                  70
                                    75
Pro Val Ile Lys Ala Ala Lys Asn Lys Lys His Val Phe Cys Glu Lys
                                 90
              85
Pro Ile Ala Leu Ser Tyr Glu Asp Cys Val Asp Met Val Lys Ala Cys
                             105
Lys Glu Ala Gly Val Thr Phe Met Ala Gly His Ile Met Asn Phe Phe
                                           125
                          120
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Asn Gly Val Gln Tyr Ala Arg Lys Leu Ile Lys Glu Gly Val Ile Gly
                       135
Glu Ile Leu Ser Cys His Thr Lys Arg Asn Gly Trp Glu Asn Lys Gln
                                       155
Glu Arg Leu Ser Trp Lys Lys Met Lys Glu Gln Ser Gly Gly His Leu
                                  170
             165
Tyr His His Ile His Glu Leu Asp Cys Val Gln His Leu Leu Gly Glu
                              185
Ile Pro Glu Thr Val Thr Met Ile Gly Gly Asn Leu Ala His Ser Gly
                         200
Pro Gly Phe Gly Asn Glu Asp Asp Met Leu Phe Met Thr Leu Glu Phe
              215
                                          220
Pro Ser Gly Lys Leu Ala Thr Leu Glu Trp Gly Ser Ala Phe Asn Trp
                                      235
        · 230
Pro Glu His Tyr Val Ile Ile Asn Gly Thr Lys Gly Ser Ile Lys Ile
                245
Asp Met Gln Glu Thr Ala Gly Ser Leu Arg Ile Gly Gly Gln Thr Lys
                                265
His Phe Leu Val His Glu Thr Gln Glu Glu Asp Asp Asp Arg Arg Lys
        275
                           280
Gly Asn Met Thr Ser Glu Met Asp Gly Ala Ile Ala Tyr Gly His Pro
                       295
Gly Lys Lys Thr Pro Leu Trp Leu Ala Ser Leu Ile Arg Lys Glu Thr
                    310
                                       315
Leu Phe Leu His Asn Ile Leu Cys Gly Ala Lys Pro Glu Glu Asp Tyr
                                  330
               325
Ile Asp Leu Leu Asn Gly Glu Ala Ala Met Ser Ala Ile Ala Thr Ala
                               345
           340
Asp Ala Ala Thr Leu Ser Arg Ser Gln Asp Arg Lys Val Lys Ile Ser
                           360
        355
Glu Ile Ile Lys His Thr Ser Val Met
. 370
                        375
<210> 430
<211> 464
<212> PRT
<213> Escherichia coli
<400> 430
Met Ser Ala Gly Lys Leu Pro Glu Gly Trp Val Ile Ala Pro Val Ser
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Thr Val Thr Thr Leu Ile Arg Gly Val Thr Tyr Lys Lys Glu Gln Ala
Ile Asn Tyr Leu Lys Asp Asp Tyr Leu Pro Leu Ile Arg Ala Asn Asn
        35
                            40
Ile Gln Asn Gly Lys Phe Asp Thr Thr Asp Leu Val Phe Val Pro Lys
                       55
Asn Leu Val Lys Glu Ser Gln Lys Ile Ser Pro Glu Asp Ile Val Ile
                    70
Ala Met Ser Ser Gly Ser Lys Ser Val Val Gly Lys Ser Ala His Gln
                                   90
His Leu Pro Phe Glu Cys Ser Phe Gly Ala Phe Cys Gly Val Leu Arg
            100
                               105
Pro Glu Lys Leu Ile Phe Ser Gly Phe Ile Ala His Phe Thr Lys Ser
                           120
                                              125
        115
Ser Leu Tyr Arg Asn Lys Ile Ser Ser Leu Ser Ala Gly Ala Asn Ile
                       135
                                           140
Asn Asn Ile Lys Pro Ala Ser Phe Asp Leu Ile Asn Ile Pro Ile Pro
                                      155
                    150
Pro Leu Ala Glu Gln Lys Ile Ile Ala Glu Lys Leu Asp Thr Leu Leu
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170
               165
Ala Gln Val Asp Ser Thr Lys Ala Arg Phe Glu Gln Ile Pro Gln Ile
                             185
          180
Leu Lys Arg Phe Arg Gln Ala Val Leu Gly Gly Ala Val Asn Gly Lys
                         200
                                            205
Leu Thr Glu Lys Trp Arg Asn Phe Glu Pro Gln His Ser Val Phe Lys
                              220
                     215
Lys Leu Asn Phe Glu Ser Ile Leu Thr Glu Leu Arg Asn Gly Leu Ser
         230
                                    235
Ser Lys Pro Asn Glu Ser Gly Val Gly His Pro Ile Leu Arg Ile Ser
           245
                                  250
Ser Val Arg Ala Gly His Val Asp Gln Asn Asp Ile Arg Phe Leu Glu
                              265
Cys Ser Glu Ser Glu Leu Asn Arg His Lys Leu Gln Asp Gly Asp Leu
                          280
Leu Phe Thr Arg Tyr Asn Gly Ser Leu Glu Phe Val Gly Val Cys Gly
                      295
                                         300
Leu Leu Lys Lys Leu Gln His Gln Asn Leu Leu Tyr Pro Asp Lys Leu
                                      315
                  310
Ile Arg Ala Arg Leu Thr Lys Asp Ala Leu Pro Glu Tyr Ile Glu Ile
                                 330
                                                    335
              325
Phe Phe Ser Ser Pro Ser Ala Arg Asn Ala Met Met Asn Cys Val Lys
           340 . 345
Thr Thr Ser Gly Gln Lys Gly Ile Ser Gly Lys Asp Ile Lys Ser Gln
                          360
Val Val Leu Leu Pro Pro Val Lys Glu Gln Ala Glu Ile Val Arg Arg
                      375
                                          380
Val Glu Gln Leu Phe Ala Tyr Ala Asp Thr Ile Glu Lys Gln Val Asn
                   390
                                   395
Asn Ala Leu Ala Arg Val Asn Asn Leu Thr Gln Ser Ile Leu Ala Lys
                       410
              405
Ala Phe Arg Gly Glu Leu Thr Ala Gln Trp Arg Ala Glu Asn Pro Asp
                             425
           420
Leu Ile Ser Gly Glu Asn Ser Ala Ala Ala Leu Leu Glu Lys Ile Lys
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Ala Glu Arg Ala Ala Ser Gly Gly Lys Lys Ala Ser Arg Lys Lys Ser
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<210> 431
<211> 529
<212> PRT
<213> Escherichia coli
Met Asn Asn Asn Leu Val Ala Lys Leu Trp Lys Leu Cys Asp Asn
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Leu Arg Asp Gly Gly Val Ser Tyr Gln Asn Tyr Val Asn Glu Leu Ala
                               25
           20
Ser Leu Leu Phe Leu Lys Met Cys Lys Glu Thr Gly Gln Glu Ala Glu
                           40
Tyr Leu Pro Glu Gly Tyr Arg Trp Asp Asp Leu Lys Ser Arg Ile Gly
                      55
                                         60
Gln Glu Gln Leu Gln Phe Tyr Arg Lys Met Leu Val His Leu Gly Glu
                   70
                                     75
Asp Asp Lys Lys Leu Val Gln Ala Val Phe His Asn Val Ser Thr Thr
                                  90
               85
Ile Thr Glu Pro Lys Gln Ile Thr Ala Leu Val Ser Asn Met Asp Ser
                              105
Leu Asp Trp Tyr Asn Gly Ala His Gly Lys Ser Arg Asp Asp Phe Gly
                          120
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Asp Met Tyr Glu Gly Leu Leu Gln Lys Asn Ala Asn Glu Thr Lys Ser
                       135
Gly Ala Gly Gln Tyr Phe Thr Pro Arg Pro Leu Ile Lys Thr Ile Ile
                   150
                                      155
His Leu Leu Lys Pro Gln Pro Arg Glu Val Val Gln Asp Pro Ala Ala
                                 170
               165
Gly Thr Ala Gly Phe Leu Ile Glu Ala Asp Arg Tyr Val Lys Ser Gln
          180
                              185
Thr Asn Asp Leu Asp Asp Leu Asp Gly Asp Thr Gln Asp Phe Gln Ile
                 200
His Arg Ala Phe Ile Gly Leu Glu Leu Val Pro Gly Thr Arg Arg Leu
            215
                                          220
Ala Leu Met Asn Cys Leu Leu His Asp Ile Glu Gly Asn Leu Asp His
                  230
                                    235
Gly Gly Ala Ile Arg Leu Gly Asn Thr Leu Gly Ser Asp Gly Glu Asn
                                   250
Leu Pro Lys Ala His Ile Val Ala Thr Asn Pro Pro Phe Gly Ser Ala
                               265
                                                270
Ala Gly Thr Asn Ile Thr Arg Thr Phe Val His Pro Thr Ser Asn Lys
                           280
Gln Leu Cys Phe Met Gln His Ile Ile Glu Thr Leu His Pro Gly Gly
                       295
Arq Ala Ala Val Val Pro Asp Asn Val Leu Phe Glu Gly Gly Lys
                   310
                                      315
Gly Thr Asp Ile Arg Arg Asp Leu Met Asp Lys Cys His Leu His Thr
               325
                                   330
Ile Leu Arg Leu Pro Thr Gly Ile Phe Tyr Ala Gln Gly Val Lys Thr
                               345
           340
Asn Val Leu Phe Phe Thr Lys Gly Thr Val Ala Asn Pro Asn Gln Asp
                           360
Lys Asn Cys Thr Asp Asp Val Trp Val Tyr Asp Leu Arg Thr Asn Met
                       375
                                          380
Pro Ser Phe Gly Lys Arg Thr Pro Phe Thr Asp Glu His Leu Gln Pro
                                      395
                   390
Phe Glu Arg Val Tyr Gly Glu Asp Pro His Gly Leu Ser Pro Arg Thr
              405
                                  410
Glu Gly Glu Trp Ser Phe Asn Ala Glu Glu Thr Glu Val Ala Asp Ser
                               425
Glu Glu Asn Lys Asn Thr Asp Gln His Leu Ala Thr Ser Arg Trp Arg
                          440
Lys Phe Ser Arg Glu Trp Ile Arg Thr Ala Lys Ser Asp Ser Leu Asp
                                          460
                       455
Ile Ser Trp Leu Lys Asp Lys Asp Ser Ile Asp Ala Asp Ser Leu Pro
                   470
                                       475
Glu Pro Asp Val Leu Ala Ala Glu Ala Met Gly Glu Leu Val Gln Ala
               485
                                   490
Leu Ser Glu Leu Asp Ala Leu Met Arg Glu Leu Gly Ala Ser Asp Glu
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Ala Asp Leu Gln Arg Gln Leu Leu Glu Glu Ala Phe Gly Gly Val Lys
Glu
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<400> 432

Met Lys Lys Glu Asn Tyr Ser Phe Lys Gln Ala Cys Ala Val Val Gly

<210> 432

<211> 98

<212> PRT

<213> Escherichia coli

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Gly Gln Ser Ala Met Ala Arg Leu Leu Gly Val Ser Pro Pro Ser Val
Asn Gln Trp Ile Lys Gly Val Arg Gln Leu Pro Ala Glu Arg Cys Pro
                            40
Ala Ile Glu Arg Ala Thr Arg Gly Glu Val Leu Cys Glu Glu Leu Arg
                       55
Pro Asp Ile Asp Trp Ser Tyr Leu Arg Arg Ser Ala Cys Cys Ser Gln
                   70
Asn Met Ser Val Lys Gln Leu Asn Asp Ser Asn Lys Ser Ser Phe Asp
His Thr
<210> 433
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<212> PRT
<213> Escherichia coli
<400> 433
Met Lys Ile Lys His Glu His Ile Glu Ser Val Leu Phe Ala Leu Ala
                                    10
Ala Glu Lys Gly Gln Ala Trp Val Ala Asn Ala Ile Thr Glu Glu Tyr
                               25
            20
Leu Arg Gln Gly Gly Glu Leu Pro Leu Val Pro Gly Lys Asp Trp
Asn Asn Gln Gln Asn Ile Tyr His Arg Trp Leu Lys Gly Glu Thr Lys
                       55
Thr Gln Arg Glu Lys Ile Gln Lys Leu Ile Pro Ala Ile Leu Ala Ile
                                       75
                   70
Leu Pro Arg Glu Leu Arg His Arg Leu Cys Ile Phe Asp Thr Leu Glu
                                   90
               85
Arg Arg Ala Leu Leu Ala Ala Gln Glu Ala Leu Ser Thr Ala Ile Asp
                                105
Ala His Asp Asp Ala Val Gln Ala Val Tyr Arg Lys Ala His Phe Ser
                            120
Gly Gly Gly Ser Ser Asp Asp Ser Val Ile Val His
    130
                        135
<210> 434
<211> 285
<212> PRT
<213> Escherichia coli
<400> 434
Met Leu Phe Val Leu Ile Leu Ser His Arg Ala Ala Ser Tyr Gly Ala
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Ile Met Ala Ala Leu Pro Tyr Met Gln Leu Tyr Ile Ala Asp Tyr Leu
Ala Asp Thr Met His Leu Ser Ala Glu Glu His Gly Ala Tyr Leu Leu
Leu Met Phe Asn Tyr Trp Gln Thr Gly Lys Pro Ile Pro Lys Asn Arg
                        55
Leu Ala Lys Ile Ala Arg Leu Thr Asn Glu Arg Trp Ala Asp Val Glu
                    70
Pro Ser Leu Gln Glu Phe Phe Cys Asp Asn Gly Glu Glu Trp Val His
Leu Arg Ile Glu Glu Asp Leu Ala Ser Val Arg Glu Lys Leu Thr Lys
                               105
Lvs Ser Ala Ala Gly Lys Ala Ser Val Gln Ala Arg Arg Ser Arg Lys
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120
      115
Glu Ala Asp Val Gln Thr Lys Gln Glu Arg Asn Leu Thr Gly Val Gln
            135
                                        140
Thr Asp Val Glu Val Val Phe Glu His Asp Val Asn Thr Lys Ala Thr
                  150
Asn Lys Asp Thr Asp Lys Asp Leu Lys Thr Asp Pro Pro Leu Asn Pro
            165
                                170
Pro Arg Gly Asn Arg Gly Val Lys Lys Phe Asp Pro Leu Asp Ile Thr
                   185
                                       190
          180
Leu Pro Asn Trp Ile Ser Val Ser Leu Trp Arg Glu Trp Val Glu Phe
                          200
Arg Gln Ala Leu Arg Lys Pro Ile Arg Thr Glu Gln Gly Ala Asn Gly
                       215
Ala Ile Arg Glu Leu Glu Lys Phe Arg Gln Gly Phe Ser Pro Glu
                   230
                                      235
Gln Val Ile Arg His Ser Ile Ala Asn Glu Tyr Gln Gly Leu Phe Ala
                                 250
               245
Pro Lys Gly Val Arg Pro Glu Thr Leu Leu Arg Gln Val Asn Thr Val
                              265
Ser Leu Pro Asp Ser Ala Ile Pro Pro Gly Phe Arg Gly
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<210> 435
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<212> PRT
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Met Lys Asn Ile Ala Thr Gly Asp Val Leu Glu Arg Ile Arg Arg Leu
Ala Pro Ser His Val Thr Ala Pro Phe Lys Thr Val Ala Glu Trp Arg
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Glu Trp Gln Leu Ser Glu Gly Gln Lys Arg Cys Glu Glu Ile Asn Arg
Gln Asn Arg Gln Leu Arg Val Glu Lys Ile Leu Asn Arg Ser Gly Ile
                     55
                                         60
Gln Pro Leu His Arg Lys Cys Ser Phe Ser Asn Tyr Gln Val Gln Asn
                   70
                                     75
Glu Gly Gln Arg Tyr Ala Leu Ser Gln Ala Lys Ser Ile Ala Asp Glu
               85
                                  90
Leu Met Thr Gly Cys Thr Asn Phe Ala Phe Ser Gly Lys Pro Gly Thr
           100
                              105
Gly Lys Asn His Leu Ala Ala Ile Gly Asn Arg Leu Leu Lys Asp
                                             125
                          120
Gly Gln Thr Val Ile Val Val Thr Val Ala Asp Val Met Ser Ala Leu
                      135
                                         140
His Ala Ser Tyr Asp Asp Gly Gln Ser Gly Glu Lys Phe Leu Arg Glu
                  150
                                     155
Leu Cys Glu Val Asp Leu Leu Val Leu Asp Glu Ile Gly Ile Gln Arg
              165
                                 170
Glu Thr Lys Asn Glu Gln Val Val Leu His Gln Ile Val Asp Arg Arg
          180
                             185
Thr Ala Ser Met Arg Ser Val Gly Met Leu Thr Asn Leu Asn Tyr Glu
                          200
Ala Met Lys Thr Leu Leu Gly Glu Arg Ile Met Asp Arg Met Thr Met
                      215
                                         220
Asn Gly Gly Arg Trp Val Asn Phe Asn Trp Glu Ser Trp Arg Pro Asn
                  230
                                     235
Val Val Gln Pro Gly Ile Ala Lys
               245
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<210> 436
<211> 203
<212> PRT
<213> Escherichia coli
Met Ser Ser Ser Gln Glu Leu Arg Ser Asn Phe Tyr Arg Glu Lys Asn
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Leu Met Glu Thr Val Phe Asp Ala Leu Lys Ala Met Gly Lys Ala Thr
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                         25
Ser Ile Glu Leu Ala Ala Arg Leu Asp Ile Ser Arg Glu Glu Val Leu
                         40
Asn Glu Leu Trp Glu Leu Lys Lys Ala Gly Phe Val Asp Lys Ser Ala
                     55
                                     60
Tyr Thr Trp Arg Val Ala Asp Asn Asn Val Gln Glu Gln Pro Ala
               70
                                  75
Gln Ala Glu Leu Pro Glu Glu Ile Thr Thr Ala Thr Val Ala Lys Ile
                                90
            85
Ser Glu Cys Asp Leu Thr Ala Thr Ile Glu Gln Arg Gly Pro Gln Thr
                            105
Ala Asp Glu Leu Ala Thr Leu Phe Gly Thr Thr Ser Arg Lys Val Ala
                        120
                                          125
Ser Thr Leu Ala Met Ala Ile Ser Lys Gly Arg Leu Ile Arg Val Asn
                     135
                                       140
Gln Gly Gly Lys Phe Arg Tyr Cys Ile Pro Gly Asp Asn Leu Pro Ala
145 150
                                    155
Glu Pro Lys Ala Ala Ser Val Ser Pro Leu Trp Leu Ser Ala Ser Ser
                      170 175
             165
Ser Ala Cys His Gly Val Leu Ile Ile Thr Val Ile Thr Pro Ser Pro
          180 185
Thr Lys Asn Ser Ala Thr Lys Met Pro Glu Asn
 195
<210> 437
<211> 101
<212> PRT
<213> Escherichia coli
<400> 437
Met Gln Met Arg Gln Arg Asp Val Ala Ala Leu Asp Ala Lys Tyr Thr
                                 10
              5
Lys Glu Leu Ala Asp Ala Lys Ala Glu Asn Asp Ala Leu Arg Asp Asp
                             25
Val Ala Ala Gly Arg Arg Leu His Ile Lys Ala Val Cys Gln Ser
                         40
                                           45
Val Arg Glu Ala Thr Thr Ala Ser Gly Val Asp Asn Ala Ala Ser Pro
                     55
Arg Leu Ala Asp Thr Ala Glu Arg Asp Tyr Phe Thr Leu Arg Glu Arg
                                    75
                 70
Leu Val Met Met Gln Ala Gln Leu Glu Gly Ala Gln Gln Tyr Ile Thr
                                90
Glu Gln Cys Leu Lys
          100
<210> 438
<211> 292
<212> PRT
<213> Escherichia coli
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Met Lys Leu Gly Phe Ile Gly Leu Gly Ile Met Gly Thr Pro Met Ala
Ile Asn Leu Ala Arg Ala Gly His Gln Leu His Val Thr Thr Ile Gly
           20
                              25
Pro Val Ala Asp Glu Leu Leu Ser Leu Gly Ala Val Ser Val Glu Thr
                          40
Ala Arg Gln Val Thr Glu Ala Ser Asp Ile Ile Phe Ile Met Val Pro
                      55
                                          60
Asp Thr Pro Gln Val Glu Glu Val Leu Phe Gly Glu Asn Gly Cys Thr
                                     75
                  70
Lys Ala Ser Leu Lys Gly Lys Thr Ile Val Asp Met Ser Ser Ile Ser
                                 90
              8.5
Pro Ile Glu Thr Lys Arg Phe Ala Arg Gln Val Asn Glu Leu Gly Gly
          100
                              105
Asp Tyr Leu Asp Ala Pro Val Ser Gly Glu Ile Gly Ala Arg Glu
                           120
                                              125
Gly Thr Leu Ser Ile Met Val Gly Gly Asp Glu Ala Val Phe Glu Arg
                       135
                                         140
Val Lys Pro Leu Phe Glu Leu Leu Gly Lys Asn Ile Thr Leu Val Gly
                   150
                                      155
Gly Asn Gly Asp Gly Gln Thr Cys Lys Val Ala Asn Gln Ile Ile Val
                                  170
Ala Leu Asn Ile Glu Ala Val Ser Glu Ala Leu Leu Phe Ala Ser Lys
                                                 190
           180
                              185
Ala Gly Ala Asp Pro Val Arg Val Arg Gln Ala Leu Met Gly Gly Phe
                          200
Ala Ser Ser Arg Ile Leu Glu Val His Gly Glu Arg Met Ile Lys Arg
                       215
                                          220
Thr Phe Asn Pro Gly Phe Lys Ile Ala Leu His Gln Lys Asp Leu Asn
                   230
                                      235
Leu Ala Leu Gln Ser Ala Lys Ala Leu Ala Leu Asn Leu Pro Asn Thr
                    250
              245
Ala Thr Cys Gln Glu Leu Phe Asn Thr Cys Ala Ala Asn Gly Gly Ser
                 265
Gln Leu Asp His Ser Ala Leu Val Gln Ala Leu Glu Leu Met Ala Asn
His Lys Leu Ala
   290
<210> 439
<211> 92
<212> PRT
<213> Escherichia coli
<400> 439
Met Asn Arg Pro Ala Ile Leu Lys Lys Ala Ala Lys Asp Val Ala
                                  10
Ser Val Leu Lys Ile Ile Phe Leu Phe Tyr Leu Phe Leu Ile Ala Arg
           20
                               25
Leu Lys Gln Arg Tyr Ser Ile Arg Glu Ile Lys Arg Asp Leu Trp Asn
                           40
Ile Arg Glu Asn Tyr Ser Ser Asn Ala Ala Ile Ala Lys Ile Tyr Cys
                       55
                                          60
Arg Lys Arg Lys Ala Ser Gly Pro Gly Lys His Leu Thr Ile Leu Pro
                   70
                                      75
Tyr Gly Trp Val Arg. Phe Ile Thr Phe Pro Ile Met
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<210> 440

<211> 437

<212> PRT <213> Escherichia coli <400> 440 Met Val Gly Gly Phe Phe Ile Leu Gly Leu Ser Thr Phe Ser Ile Met 10 Leu Ala Ile Ile Leu Ser Ala Phe Phe Ile Ala Ala Val Met Val Leu 25 20 Asn Gly Ala Ala Gly Ser Lys Tyr Gly Val Pro Phe Ala Met Ile Leu 35 . 40 Arg Ala Ser Tyr Gly Val Arg Gly Ala Leu Phe Pro Gly Leu Leu Arg 55 Gly Gly Ile Ala Ala Ile Met Trp Phe Gly Leu Gln Cys Tyr Ala Gly 70 75 Ser Leu Ala Cys Leu Ile Leu Ile Gly Lys Ile Trp Pro Gly Phe Leu 90 85 Thr Leu Gly Gly Asp Phe Thr Leu Leu Gly Leu Ser Leu Pro Gly Leu 105 Ile Thr Phe Leu Ile Phe Trp Leu Val Asn Val Gly Ile Gly Phe Gly 125 120 Gly Gly Lys Val Leu Asn Lys Phe Thr Ala Ile Leu Asn Pro Cys Ile 135 140 Tyr Ile Val Phe Gly Gly Met Ala Ile Trp Ala Ile Ser Leu Val Gly 150 155 Ile Gly Pro Ile Phe Asp Tyr Ile Pro Ser Gly Ile Gln Lys Ala Glu 170 175 165 Asn Gly Gly Phe Leu Phe Leu Val Val Ile Asn Ala Val Val Ala Val 185 180 Trp Ala Ala Pro Ala Val Ser Ala Ser Asp Phe Thr Gln Asn Ala His 200 Ser Phe Arg Glu Gln Ala Leu Gly Gln Thr Leu Gly Leu Val Val Ala 220 215 Tyr Ile Leu Phe Ala Val Ala Gly Val Cys Ile Ile Ala Gly Ala Ser 225 230 235 Ile His Tyr Gly Ala Asp Thr Trp Asn Val Leu Asp Ile Val Gln Arg 245 250 Trp Asp Ser Leu Phe Ala Ser Phe Phe Ala Val Leu Val Ile Leu Met 260 265 Thr Thr Ile Ser Thr Asn Ala Thr Gly Asn Ile Ile Pro Ala Gly Tyr 275 280 Gln Ile Ala Ala Ile Ala Pro Thr Lys Leu Thr Tyr Lys Asn Gly Val 300 295 Leu Ile Ala Ser Ile Ile Ser Leu Leu Ile Cys Pro Trp Lys Leu Met 310 315 Glu Asn Gln Asp Ser Ile Tyr Leu Phe Leu Asp Ile Ile Gly Gly Met 325 330 Leu Gly Pro Val Ile Gly Val Met Met Ala His Tyr Phe Val Val Met 345 340 Arg Gly Gln Ile Asn Leu Asp Glu Leu Tyr Thr Ala Pro Gly Asp Tyr 360 365 Lys Tyr Tyr Asp Asn Gly Phe Asn Leu Thr Ala Phe Ser Val Thr Leu 375 380 Val Ala Val Ile Leu Ser Leu Gly Gly Lys Phe Ile His Phe Met Glu 390 395 Pro Leu Ser Arg Val Ser Trp Phe Val Gly Val Ile Val Ala Phe Ala 410 415 405 Ala Tyr Ala Leu Leu Lys Lys Arg Thr Thr Ala Glu Lys Thr Gly Glu 425 420 Gln Lys Thr Ile Gly

435

<210> 441 <211> 464 <212> PRT <213> Escherichia coli <400> 441 Met Leu Leu Asp Ala Cys Ser Gln Met Cys Pro Ser Phe Arg Arg 10 Phe Gln Thr Val Phe His Asn Ser Ser Ile Phe Leu Pro Tyr Trp Leu 25 Ala Thr Leu Val Ser Phe Arg Glu Thr Phe Gln Glu Glu Lys Leu Leu 40 Thr Met Lys Gly Ser Tyr Lys Ser Arg Trp Val Ile Val Ile Val Val 55 Val Ile Ala Ala Ile Ala Ala Phe Trp Phe Trp Gln Gly Arg Asn Asp 75 70 Ser Arg Ser Ala Ala Pro Gly Ala Thr Lys Gln Ala Gln Gln Ser Pro 90 85 Ala Gly Gly Arg Arg Gly Met Arg Ser Gly Pro Leu Ala Pro Val Gln 105 Ala Ala Thr Ala Val Glu Gln Ala Val Pro Arg Tyr Leu Thr Gly Leu 120 125 Gly Thr Ile Thr Ala Ala Asn Thr Val Thr Val Arg Ser Arg Val Asp 130 135 140 Gly Gln Leu Ile Ala Leu His Phe Gln Glu Gly Gln Gln Val Lys Ala 150 155 Gly Asp Leu Leu Ala Glu Ile Asp Pro Ser Gln Phe Lys Val Ala Leu 170 165 Ala Gln Ala Gln Gly Gln Leu Ala Lys Asp Lys Ala Thr Leu Ala Asn 180 185 Ala Arg Arg Asp Leu Ala Arg Tyr Gln Gln Leu Ala Lys Thr Asn Leu 200 Val Ser Arg Gln Glu Leu Asp Ala Gln Gln Ala Leu Val Ser Glu Thr 215 220 Glu Gly Thr Ile Lys Ala Asp Glu Ala Ser Val Ala Ser Ala Gln Leu 230 235 Gln Leu Asp Trp Ser Arg Ile Thr Ala Pro Val Asp Gly Arg Val Gly 245 250 Leu Lys Gln Val Asp Val Gly Asn Gln Ile Ser Ser Gly Asp Thr Thr 265 270 Gly Ile Val Val Ile Thr Gln Thr His Pro Ile Asp Leu Val Phe Thr 280 285 Leu Pro Glu Ser Asp Ile Ala Thr Val Val Gln Ala Gln Lys Ala Gly 295 300 Lys Pro Leu Val Val Glu Ala Trp Asp Arg Thr Asn Ser Lys Lys Leu 310 315 Ser Glu Gly Thr Leu Leu Ser Leu Asp Asn Gln Ile Asp Ala Thr Thr 330 Gly Thr Ile Lys Val Lys Ala Arg Phe Asn Asn Gln Asp Asp Ala Leu 345 340 Phe Pro Asn Gln Phe Val Asn Ala Arg Met Leu Val Asp Thr Glu Gln 360 365 Asn Ala Val Val Ile Pro Thr Ala Ala Leu Gln Met Gly Asn Glu Gly 375 380 His Phe Val Trp Val Leu Asn Ser Glu Asn Lys Val Ser Lys His Leu 390 395 Val Thr Pro Gly Ile Gln Asp Ser Gln Lys Val Val Ile Arg Ala Gly 405 410

-394-

Ile Ser Ala Gly Asp Arg Val Val Thr Asp Gly Ile Asp Arg Leu Thr 425 Glu Gly Ala Lys Val Glu Val Val Glu Ala Gln Ser Ala Thr Thr Pro 440 Glu Glu Lys Ala Thr Ser Arg Glu Tyr Ala Lys Lys Gly Ala Arg Ser <210> 442 <211> 1040 <212> PRT <213> Escherichia coli <400> 442 Met Gln Val Leu Pro Pro Ser Ser Thr Gly Gly Pro Ser Arg Leu Phe 10 Ile Met Arg Pro Val Ala Thr Thr Leu Leu Met Val Ala Ile Leu Leu Ala Gly Ile Ile Gly Tyr Arg Ala Leu Pro Val Ser Ala Leu Pro Glu 40 Val Asp Tyr Pro Thr Ile Gln Val Val Thr Leu Tyr Pro Gly Ala Ser 55 60 Pro Asp Val Met Thr Ser Ala Val Thr Ala Pro Leu Glu Arg Gln Phe 70 . . 75 Gly Gln Met Ser Gly Leu Lys Gln Met Ser Ser Gln Ser Ser Gly Gly 90 Ala Ser Val Ile Thr Leu Gln Phe Gln Leu Thr Leu Pro Leu Asp Val 100 105 110 Ala Glu Gln Glu Val Gln Ala Ala Ile Asn Ala Ala Thr Asn Leu Leu 120 125 Pro Ser Asp Leu Pro Asn Pro Pro Val Tyr Ser Lys Val Asn Pro Ala 135 Asp Pro Pro Ile Met Thr Leu Ala Val Thr Ser Thr Ala Met Pro Met 150 155 Thr Gln Val Glu Asp Met Val Glu Thr Arg Val Ala Gln Lys Ile Ser 165 170 Gln Ile Ser Gly Val Gly Leu Val Thr Leu Ser Gly Gly Gln Arg Pro 180 185 Ala Val Arg Val Lys Leu Asn Ala Gln Ala Ile Ala Ala Leu Gly Leu 195 Thr Ser Glu Thr Val Arg Thr Ala Ile Thr Gly Ala Asn Val Asn Ser 215 220 Ala Lys Gly Ser Leu Asp Gly Pro Ser Arg Ala Val Thr Leu Ser Ala 230 235 Asn Asp Gln Met Gln Ser Ala Glu Glu Tyr Arg Gln Leu Ile Ile Ala 245 250 Tyr Gln Asn Gly Ala Pro Ile Arg Leu Gly Asp Val Ala Thr Val Glu 265 Gln Gly Ala Glu Asn Ser Trp Leu Gly Ala Trp Ala Asn Lys Glu Gln 280 285 Ala Ile Val Met Asn Val Gln Arg Gln Pro Gly Ala Asn Ile Ile Ser 295 300 Thr Ala Asp Ser Ile Arg Gln Met Leu Pro Gln Leu Thr Glu Ser Leu 310 315 Pro Lys Ser Val Lys Val Thr Val Leu Ser Asp Arg Thr Thr Asn Ile 325 330 Arg Ala Ser Val Asp Asp Thr Gln Phe Glu Leu Met Met Ala Ile Ala 345 Leu Val Val Met Ile Ile Tyr Leu Phe Leu Arg Asn Ile Pro Ala Thr 360 365 Ile Ile Pro Gly Val Ala Val Pro Leu Ser Leu Ile Gly Thr Phe Ala

Val Met Val Phe Leu Asp Phe Ser Ile Asn Asn Leu Thr Leu Met Ala Leu Thr Ile Ala Thr Gly Phe Val Val Asp Asp Ala Ile Val Val Ile Glu Asn Ile Ser Arg Tyr Ile Glu Lys Gly Glu Lys Pro Leu Ala Ala Ala Leu Lys Gly Ala Gly Glu Ile Gly Phe Thr Ile Ile Ser Leu Thr Phe Ser Leu Ile Ala Val Leu Ile Pro Leu Leu Phe Met Gly Asp Ile Val Gly Arg Leu Phe Arg Glu Phe Ala Ile Thr Leu Ala Val Ala Ile Leu Ile Ser Ala Val Val Ser Leu Thr Leu Thr Pro Met Met Cys Ala Arq Met Leu Ser Gln Glu Ser Leu Arg Lys Gln Asn Arg Phe Ser Arg Ala Ser Glu Lys Met Phe Asp Arg Ile Ile Ala Ala Tyr Gly Arg Gly Leu Ala Lys Val Leu Asn His Pro Trp Leu Thr Leu Ser Val Ala Leu Ser Thr Leu Leu Ser Val Leu Leu Trp Val Phe Ile Pro Lys Gly Phe Phe Pro Val Gln Asp Asn Gly Ile Ile Gln Gly Thr Leu Gln Ala Pro Gln Ser Ser Phe Ala Asn Met Ala Gln Arg Gln Arg Gln Val Ala Asp Val Ile Leu Gln Asp Pro Ala Val Gln Ser Leu Thr Ser Phe Val Gly Val Asp Gly Thr Asn Pro Ser Leu Asn Ser Ala Arg Leu Gln Ile Asn Leu Lys Pro Leu Asp Glu Arg Asp Asp Arg Val Gln Lys Val Ile Ala Arg Leu Gln Thr Ala Val Asp Lys Val Pro Gly Val Asp Leu Phe Leu Gln Pro Thr Gln Asp Leu Thr Ile Asp Thr Gln Val Ser Arg Thr Gln Tyr Gln Phe Thr Leu Gln Ala Thr Ser Leu Asp Ala Leu Ser 680 685 Thr Trp Val Pro Gln Leu Met Glu Lys Leu Gln Gln Leu Pro Gln Leu Ser Asp Val Ser Ser Asp Trp Gln Asp Lys Gly Leu Val Ala Tyr Val Asn Val Asp Arg Asp Ser Ala Ser Arg Leu Gly Ile Ser Met Ala Asp Val Asp Asn Ala Leu Tyr Asn Ala Phe Gly Gln Arg Leu Ile Ser Thr Ile Tyr Thr Gln Ala Asn Gln Tyr Arg Val Val Leu Glu His Asn Thr Glu Asn Thr Pro Gly Leu Ala Ala Leu Asp Thr Ile Arg Leu Thr Ser Ser Asp Gly Gly Val Val Pro Leu Ser Ser Ile Ala Lys Ile Glu Gln Arg Phe Ala Pro Leu Ser Ile Asn His Leu Asp Gln Phe Pro Val Thr Thr Ile Ser Phe Asn Val Pro Asp Asn Tyr Ser Leu Gly Asp Ala Val Gln Ala Ile Met Asp Thr Glu Lys Thr Leu Asn Leu Pro Val Asp Ile Thr Thr Gln Phe Gln Gly Ser Thr Leu Ala Phe Gln Ser Ala Leu Gly

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855
Ser Thr Val Trp Leu Ile Val Ala Ala Val Val Ala Met Tyr Ile Val
         870
                          875
Leu Gly Ile Leu Tyr Glu Ser Phe Ile His Pro Ile Thr Ile Leu Ser
                              890
            885
Thr Leu Pro Thr Ala Gly Val Gly Ala Leu Leu Ala Leu Leu Ile Ala
                           905
Gly Ser Glu Leu Asp Val Ile Ala Ile Ile Gly Ile Ile Leu Leu Ile
  915 920
Gly Ile Val Lys Lys Asn Ala Ile Met Met Ile Asp Phe Ala Leu Ala
                                     940
                  935
Ala Glu Arg Glu Gln Gly Met Ser Pro Arg Glu Ala Ile Tyr Gln Ala
                950
                                  955
Cys Leu Leu Arg Phe Arg Pro Ile Leu Met Thr Thr Leu Ala Ala Leu
             965
                              970
Leu Gly Ala Leu Pro Leu Met Leu Ser Thr Gly Val Gly Ala Glu Leu
                          985
Arg Arg Pro Leu Gly Ile Gly Met Val Gly Gly Leu Ile Val Ser Gln
                      1000 1005
Val Leu Thr Leu Phe Thr Thr Pro Val Ile Tyr Leu Leu Phe Asp Arg
  1010 1015 1020
Leu Ala Leu Trp Thr Lys Ser Arg Phe Ala Arg His Glu Glu Glu Ala
1025 1030 1035
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Met Lys Phe Phe Ala Leu Phe Ile Tyr Arg Pro Val Ala Thr Ile Leu
Leu Ser Val Ala Ile Thr Leu Cys Gly Ile Leu Gly Phe Arg Met Leu
                    25
Pro Val Ala Pro Leu Pro Gln Val Asp Phe Pro Val Ile Ile Val Ser
                               45
                    40
Ala Ser Leu Pro Gly Ala Ser Pro Glu Thr Met Ala Ser Ser Val Ala
          55
                                   60
Thr Pro Leu Glu Arg Ser Leu Gly Arg Ile Ala Gly Val Ser Glu Met
Thr Ser Ser Ser Leu Gly Ser Thr Arg Ile Ile Leu Gln Phe Asp
                               90
Phe Asp Arg Asp Ile Asn Gly Ala Ala Arg Asp Val Gln Ala Ala Ile
                          105
          100
Asn Ala Ala Gln Ser Leu Leu Pro Ser Gly Met Pro Ser Arg Pro Thr
                       120
Tyr Arg Lys Ala Asn Pro Ser Asp Ala Pro Ile Met Ile Leu Thr Leu
                    135
                                      140
Thr Ser Asp Thr Tyr Ser Gln Gly Glu Leu Tyr Asp Phe Ala Ser Thr
                150
                                  155
Gln Leu Ala Pro Thr Ile Ser Gln Ile Asp Gly Val Gly Asp Val Asp
                              170
                                                175
             165 .
Val Gly Gly Ser Ser Leu Pro Ala Val Arg Val Gly Leu Asn Pro Gln
         180
                         185
                                            190
Ala Leu Phe Asn Gln Gly Val Ser Leu Asp Asp Val Arg Thr Ala Val
    195
                        200
                                · 205
Ser Asn Ala Asn Val Arg Lys Pro Gln Gly Ala Leu Glu Asp Gly Thr
                                    220
                    215
His Arg Trp Gln Ile Gln Thr Asn Asp Glu Leu Lys Thr Ala Ala Glu
                 230
                                 235
```

Tyr	Gln	Pro	Leu	Ile 245	Ile	His	Tyr	Asn	Asn 250	Gly	Gly	Ala	Val	Arg 255	Leu
Gly	Asp	Val	Ala 260	Thr	Val	Thr	Asp	Ser 265	Val	Gln	Asp	Val	Arg 270	Asn	Ala
Gly	Met	Thr 275	Asn	Ala	Lys	Pro	Ala 280	Ile	Leu	Leu	Met	Ile 285	Arg	Lys	Leu
Pro	Glu 290		Asn	Ile	Ile	Gln 295		Val	Asp	Ser	Ile 300		Ala	Lys	Leu
Pro 305		Leu	Gln	Glu	Thr 310		Pro	Ala	Ala	Ile 315		Leu	Gln	Ile	Ala 320
	Asp	Arg	Ser	Pro 325		Ile	Arg	Ala	Ser 330		Glu	Glu	Val	Glu 335	
Thr	Leu	Ile	11e 340		Val	Ala	Leu	Val 345		Leu	Val	Val	Phe 350		Phe
Leu	Arg	Ser 355	Gly	Arg	Ala	Thr	Ile 360		Pro	Ala	Val	Ser 365		Pro	Val
Ser	Leu 370		Gly	Thr	Phe	Ala 375		Met	Tyr	Leu	Cys 380		Phe	Ser	Leu
Asn 385		Leu	Ser	Leu	Met 390	Ala	Leu	Thr	Ile	Ala 395	Thr	Gly	Phe	Val	Val 400
	Asp	Ala	Ile	Val 405	Val	Leu	Glu	Asn	Ile 410	Ala	Arg	His	Leu	Glu 415	Ala
Gly	Met	Lys	Pro 420	Leu	Gln	Ala	Ala	Leu 425	Gln	Gly	Thr	Arg	Glu 430	Val	Gly
Phe	Thr	Val 435	Leu	Ser	Met	Ser	Leu 440	Ser	Leu	Val	Ala	Val 445	Phe	Leu	Pro
Leu	Leu 450	Leu	Met	Gly	Gly	Leu 455	Pro	Gly	Arg	Leu	Leu 460	Arg	Glu	Phe	Ala
Val 465	Thr	Leu	Ser	Val	Ala 470	Ile	Gly	Ile	Ser	Leu 475	Leu	Val	Ser	Leu	Thr 480
Leu	Thr	Pro	Met	Met 485	Суѕ	Gly	Trp	Met	Leu 490	Lys	Ala	Ser	Lys	Pro 495	Arg
Glu	Gln	Lys	Arg 500	.Leu	Arg	Gly	Phe	Gly 505	Arg	Met	Leu	Val	Ala 510	Leu	Gln
	_	515	Gly	_			520	_				525		_	
	530		Val			535					540				
Ile 545	Ser	Ile	Pro	Lys	Thr 550	Phe	Phe	Pro	Glu	Gln 555	Asp	Thr	Gly	Val	Leu 560
	_	_	Ile	565					570					575	_
Gly	Lys	Leu	Gln 580			Met				Arg	Asp	Asp	Pro 590	Ala	Val
Asp	Asn	Val 595	Thr	Gly	Phe	Thr	Gly 600	Gly	Ser	Arg	Val	Asn 605	Ser	Gly	Met
Met	Phe 610	Ile	Thr	Leu	Lys	Pro 615	Arg	Asp	Glu	Arg	Ser 620	Glu	Thr	Ala	Gln
625			Asp		630					635					640
			Leu	645					650					655	
Ser	Asn	Ala	Ser	Tyr	Gln	Tyr	Thr	665		Ser			670	Ala	Ala
			660												
		Glu 675	Trp	Glu	Pro	Lys	Ile 680	Arg	Lys	Lys	Leu	Ala 685	Thr	Leu	Pro
Leu Glu	Arg Leu 690	675 Ala	Trp Asp	Val	Asn	Ser 695	680 Asp	Gln	Gln	Asp	Asn 700	685 Gly	Ala	Glu	Met
Leu Glu	Arg Leu 690	675 Ala	Trp	Val	Asn	Ser 695	680 Asp	Gln	Gln	Asp	Asn 700	685 Gly	Ala	Glu	Met

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Gln Ala Ala Asn Ser Leu Leu Asn Asn Ala Phe Gly Gln Arg Gln Ile
              725
                    730
Ser Thr Ile Tyr Gln Pro Met Asn Gln Tyr Lys Val Val Met Glu Val
           740
                             745
Asp Pro Arg Tyr Thr Gln Asp Ile Ser Ala Leu Glu Lys Met Phe Val
                          760
Ile Asn Asn Glu Gly Lys Ala Ile Pro Leu Ser Tyr Phe Ala Lys Trp
                      775
                                         780
Gln Pro Ala Asn Ala Pro Leu Ser Val Asn His Gln Gly Leu Ser Ala
                 790 795
Ala Ser Thr Ile Ser Phe Asn Leu Pro Thr Gly Lys Ser Leu Ser Asp
                                 810
              805
Ala Ser Ala Ala Ile Asp Arg Ala Met Thr Gln Leu Gly Val Pro Ser
                             825
Thr Val Arg Gly Ser Phe Ala Gly Thr Ala Gln Val Phe Gln Glu Thr
                         840
                                            845
Met Asn Ser Gln Val Ile Leu Ile Ile Ala Ala Ile Ala Thr Val Tyr
                     855
                                        860
Ile Val Leu Gly Ile Leu Tyr Glu Ser Tyr Val His Pro Leu Thr Ile
                 870
                                     875
Leu Ser Thr Leu Pro Ser Ala Gly Val Gly Ala Leu Leu Ala Leu Glu
            885
                                890
Leu Phe Asn Ala Pro Phe Ser Leu Ile Ala Leu Ile Gly Ile Met Leu
        900 .905
Leu Ile Gly Ile Val Lys Lys Asn Ala Ile Met Met Val Asp Phe Ala
                         920
Leu Glu Ala Gln Arg His Gly Asn Leu Thr Pro Gln Glu Ala Ile Phe
                     935
Gln Ala Cys Leu Leu Arg Phe Arg Pro Ile Met Met Thr Thr Leu Ala
         950
                                    955
Ala Leu Phe Gly Ala Leu Pro Leu Val Leu Ser Gly Gly Asp Gly Ser
             965
                                970
Glu Leu Arg Gln Pro Leu Gly Ile Thr Ile Val Gly Gly Leu Val Met
                             985
Ser Gln Leu Leu Thr Leu Tyr Thr Thr Pro Val Val Tyr Leu Phe Phe
                          1000
                                            1005
Asp Arg Leu Arg Leu Arg Phe Ser Arg Lys Pro Lys Gln Thr Val Thr
                      1015
                                         1020
Glu
1025
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<211> 471
<212> PRT
<213> Escherichia coli
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Phe Gly Phe Phe Met Gln Ser Leu Asp Thr Thr Ile Val Asn Thr Ala
Leu Pro Ser Met Ala Gln Ser Leu Gly Glu Ser Pro Leu His Met His
                          40
Met Val Ile Val Ser Tyr Val Leu Thr Val Ala Val Met Leu Pro Ala
                                  . 60
                     55
Ser Gly Trp Leu Ala Asp Lys Val Gly Val Arg Asn Ile Phe Phe Thr
                  70
                                     75
Ala Ile Val Leu Phe Thr Leu Gly Ser Leu Phe Cys Ala Leu Ser Gly
Thr Leu Asn Glu Leu Leu Leu Ala Arg Ala Leu Gln Gly Val Gly Gly
```

```
100
                              105
Ala Met Met Val Pro Val Gly Arg Leu Thr Val Met Lys Ile Val Pro
                          120
Arg Glu Gln Tyr Met Ala Ala Met Thr Phe Val Thr Leu Pro Gly Gln
                      135
                                         140
Val Gly Pro Leu Leu Gly Pro Ala Leu Gly Gly Leu Leu Val Glu Tyr
        150
                                     155
Ala Ser Trp His Trp Ile Phe Leu Ile Asn Ile Pro Val Gly Ile Ile
              165
                                170
Gly Ala Ile Ala Thr Leu Leu Leu Met Pro Asn Tyr Thr Met Gln Thr
          180
                             185
Arg Arg Phe Asp Leu Ser Gly Phe Leu Leu Leu Ala Val Gly Met Ala
                          200
       195
Val Leu Thr Leu Ala Leu Asp Gly Ser Lys Gly Thr Gly Leu Ser Pro
                       215
                                         220
Leu Thr Ile Ala Gly Leu Val Ala Val Gly Val Val Ala Leu Val Leu
                   230
                                      235
Tyr Leu Leu His Ala Arg Asn Asn Asn Arg Ala Leu Phe Ser Leu Lys
              245
                                 250
Leu Phe Arg Thr Arg Thr Phe Ser Leu Gly Leu Ala Gly Ser Phe Ala
                              265
Gly Arg Ile Gly Ser Gly Met Leu Pro Phe Met Thr Pro Val Phe Leu
                         280
                                            285
Gln Ile Gly Leu Gly Phe Ser Pro Phe His Ala Gly Leu Met Met Ile
                   295
                                        300
Pro Met Val Leu Gly Ser Met Gly Met Lys Arg Ile Val Val Gln Val
                   310
                                     315
Val Asn Arg Phe Gly Tyr Arg Arg Val Leu Val Ala Thr Thr Leu Gly
               325
                                  330
Leu Ser Leu Val Thr Leu Leu Phe Met Thr Thr Ala Leu Leu Gly Trp
                             345
           340
Tyr Tyr Val Leu Pro Phe Val Leu Phe Leu Gln Gly Met Val Asn Ser
                       360
                                            365
Thr Arg Phe Ser Ser Met Asn Thr Leu Thr Leu Lys Asp Leu Pro Asp
                   375
                               380
Asn Leu Ala Ser Ser Gly Asn Ser Leu Leu Ser Met Ile Met Gln Leu
                  390
                                     395
Ser Met Ser Ile Gly Val Thr Ile Ala Gly Leu Leu Gly Leu Phe
             405 410
Gly Ser Gln His Val Ser Val Asp Ser Gly Thr Thr Gln Thr Val Phe
                              425
Met Tyr Thr Trp Leu Ser Met Ala Leu Ile Ile Ala Leu Pro Ala Phe
                          440
Ile Phe Ala Arg Val Pro Asn Asp Thr His Gln Asn Val Ala Ile Ser
                       455
Arg Arg Lys Arg Ser Ala Gln
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<212> PRT
<213> Escherichia coli
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Met Ile Ala Phe Glu Val Leu Lys Trp Ala Gly Ala Ala Tyr Leu Ile
                                  10
Trp Leu Gly Ile Gln Gln Trp Arg Ala Ala Gly Ala Ile Asp Leu Lys
                              25
Ser Leu Ala Ser Thr Gln Ser Arg Arg His Leu Phe Gln Arg Ala Val
                          40
```

```
Phe Val Asn Leu Thr Asn Pro Lys Ser Ile Val Phe Leu Ala Ala Leu
        55 60
Phe Pro Gln Phe Ile Met Pro Gln Gln Pro Gln Leu Met Gln Tyr Ile
      70
                  75 80
Val Leu Gly Val Thr Thr Ile Val Val Asp Ile Ile Val Met Ile Gly
Tyr Ala Thr Leu Ala Gln Arg Ile Ala Leu Trp Ile Lys Gly Pro Lys
                     105 110
Gln Met Lys Ala Leu Asn Lys Ile Phe Gly Ser Leu Phe Met Leu Val
  115 120
Gly Ala Leu Leu Ala Ser Ala Arg His Ala
  130
                 135
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<211> 257
<212> PRT
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Met Ala Arg Lys Trp Leu Asn Leu Phe Ala Gly Ala Ala Leu Ser Phe
Ala Val Ala Gly Asn Ala Leu Ala Asp Glu Gly Lys Ile Thr Val Phe
        20
                       25.
Ala Ala Ala Ser Leu Thr Asn Ala Met Gln Asp Ile Ala Thr Gln Phe
                   40
                                  45
Lys Lys Glu Lys Gly Val Asp Val Val Ser Ser Phe Ala Ser Ser Ser
               55
Thr Leu Ala Arg Gln Ile Glu Ala Gly Ala Pro Ala Asp Leu Phe Ile
Ser Ala Asp Gln Lys Trp Met Asp Tyr Ala Val Asp Lys Lys Ala Ile
        85 90 95
Asp Thr Ala Thr Arg Gln Thr Leu Leu Gly Asn Ser Leu Val Val
   100 105 110
Ala Pro Lys Ala Ser Val Gln Lys Asp Phe Thr Ile Asp Ser Lys Thr
115 120
                         125
Asn Trp Thr Ser Leu Leu Asn Gly Gly Arg Leu Ala Val Gly Asp Pro
 130 135
                               140
Glu His Val Pro Ala Gly Ile Tyr Ala Lys Glu Ala Leu Gln Lys Leu
145 150 155
Gly Ala Trp Asp Thr Leu Ser Pro Lys Leu Ala Pro Ala Glu Asp Val
           165 170 175
Arg Gly Ala Leu Ala Leu Val Glu Arg Asn Glu Ala Pro Leu Gly Ile
        180 185 190
Val Tyr Gly Ser Asp Ala Val Ala Ser Lys Gly Val Lys Val Val Ala
                    200
Thr Phe Pro Glu Asp Ser His Lys Lys Val Glu Tyr Pro Val Ala Val
                        220
  210 215
Val Glu Gly His Asn Asn Ala Thr Val Lys Ala Phe Tyr Asp Tyr Leu
225 230 235
Lys Gly Pro Gln Ala Ala Glu Ile Phe Lys Arg Tyr Gly Phe Thr Ile
<210> 447
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<211> 229

<212> PRT

<213> Escherichia coli

<400> 447

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Met Ile Leu Thr Asp Pro Glu Trp Gln Ala Val Leu Leu Ser Leu Lys
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Val Ser Ser Leu Ala Val Leu Phe Ser Leu Pro Phe Gly Ile Phe Phe
Ala Trp Leu Leu Val Arg Cys Thr Phe Pro Gly Lys Ala Leu Leu Asp
                           40
Ser Val Leu His Leu Pro Leu Val Leu Pro Pro Val Val Val Gly Tyr
                       55
Leu Leu Val Ser Met Gly Arg Arg Gly Phe Ile Gly Glu Arg Leu
                  70
Tyr Asp Trp Phe Gly Ile Thr Phe Ala Phe Ser Trp Arg Gly Ala Val
                                  90
Leu Ala Ala Ala Val Met Ser Phe Pro Leu Met Val Arg Ala Ile Arg
                              105
          100
Leu Ala Leu Glu Gly Val Asp Val Lys Leu Glu Gln Ala Ala Arg Thr
                           120
Leu Gly Ala Gly Arg Trp Arg Val Phe Phe Thr Ile Thr Leu Pro Leu
                       135
                                           140
Thr Leu Pro Gly Ile Ile Val Gly Thr Val Leu Ala Phe Ala Arg Ser
                                      155
                   150
Leu Gly Glu Phe Gly Ala Thr Ile Thr Phe Val Ser Asn Ile Pro Gly
                                   170
              165
Glu Thr Arg Thr Ile Pro Ser Ala Met Tyr Thr Leu Ile Gln Thr Pro
                               185
Gly Gly Glu Ser Gly Ala Ala Arg Leu Cys Ile Ile Ser Ile Ala Leu
                                              205
                          200
Ala Met Ile Ser Leu Leu Ile Ser Glu Trp Leu Ala Arg Ile Ser Arg
                      215
Glu Arg Ala Gly Arg
225
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Ile Asn Glu Thr Leu Pro Ala Asn Gly Ile Thr Ala Ile Phe Gly Val
                               25
Ser Gly Ala Gly Lys Thr Ser Leu Ile Asn Ala Ile Ser Gly Leu Thr
                          40
Arg Pro Gln Lys Gly Arg Ile Val Leu Asn Gly Arg Val Leu Asn Asp
Ala Glu Lys Gly Ile Cys Leu Thr Pro Glu Lys Arg Arg Val Gly Tyr
                   70
                                      75
Val Phe Gln Asp Ala Arg Leu Phe Pro His Tyr Lys Val Arg Gly Asn
                                   90
                85
Leu Arg Tyr Gly Met Ser Lys Ser Met Val Asp Gln Phe Asp Lys Leu
                               105
Val Ala Leu Leu Gly Ile Glu Pro Leu Leu Asp Arg Leu Pro Gly Ser
                           120
                                              125
Leu Ser Gly Gly Glu Lys Gln Arg Val Ala Ile Gly Arg Ala Leu Leu
                       135
                                          140
Thr Ala Pro Glu Leu Leu Leu Asp Glu Pro Leu Ala Ser Leu Asp
                                    155
                  150
Ile Pro Arg Lys Arg Glu Leu Leu Pro Tyr Leu Gln Arg Leu Thr Arg
               165
                                   170
Glu Ile Asn Ile Pro Met Leu Tyr Val Ser His Ser Leu Asp Glu Ile
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185
Leu His Leu Ala Asp Arg Val Met Val Leu Glu Asn Gly Gln Val Lys
                               205
                200
Ala Phe Gly Ala Leu Glu Glu Val Trp Gly Ser Ser Val Met Asn Pro
                   215
                                    220
Trp Leu Pro Lys Glu Gln Gln Ser Ser Ile Leu Lys Val Thr Val Leu
       230
                               235
Glu His His Pro His Tyr Ala Met Thr Ala Leu Ala Leu Gly Asp Gln
            245 . 250 255
His Leu Trp Val Asn Lys Leu Asp Glu Pro Leu Gln Ala Ala Leu Arg
         260 . 265
Ile Arg Ile Gln Ala Ser Asp Val Ser Leu Val Leu Gln Pro Pro Gln
     275 280
Gln Thr Ser Ile Arg Asn Val Leu Arg Ala Lys Val Val Asn Ser Tyr
 290 295
Asp Asp Asn Gly Gln Val Glu Val Glu Leu Glu Val Gly Gly Lys Thr
                 310
                                 315
Leu Trp Ala Arg Ile Ser Pro Trp Ala Arg Asp Glu Leu Ala Ile Lys
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                             330 . 335
Pro Gly Leu Trp Leu Tyr Ala Gln Ile Lys Ser Val Ser Ile Thr Ala
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<211> 168
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Ala Asp Thr Lys Thr Gly Gly Phe Met Asn Arg Thr Ile Leu Val Pro
          20
                           25
Ile Asp Ile Ser Asp Ser Glu Leu Thr Gln Arg Val Ile Ser His Val
                       40
                                        45
Glu Glu Glu Ala Lys Ile Asp Asp Ala Glu Val His Phe Leu Thr Val
                  55
Ile Pro Ser Leu Pro Tyr Tyr Ala Ser Leu Gly Leu Ala Tyr Ser Ala
                               75
Glu Leu Pro Ala Met Asp Asp Leu Lys Ala Glu Ala Lys Ser Gln Leu
                             90 95
Glu Glu Ile Ile Lys Lys Phe Lys Leu Pro Thr Asp Arg Val His Val
                         105 110
His Val Glu Glu Gly Ser Pro Lys Asp Arg Ile Leu Glu Leu Ala Lys
                     120 125
Lys Ile Pro Ala His Met Ile Ile Ile Ala Ser His Arg Pro Asp Ile
                            140
                   135
Thr Thr Tyr Leu Leu Gly Ser Asn Ala Ala Ala Val Val Arg His Ala
       150
                               155
Glu Cys Ser Val Leu Val Val Arg
             165
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<212> PRT
<213> Escherichia coli
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1 5
Gly Ala Ala His Ala Ala Glu Val Tyr Asn Lys Asp Gly Asn Lys Leu
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25

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Asp Leu Tyr Gly Lys Val Asp Gly Leu His Tyr Phe Ser Asp Asn Ser
                          40
Ala Lys Asp Gly Asp Gln Ser Tyr Ala Arg Leu Gly Phe Lys Gly Glu
                     55
Thr Gln Ile Asn Asp Gln Leu Thr Gly Tyr Gly Gln Trp Glu Tyr Asn
        70
Ile Gln Ala Asn Asn Thr Glu Ser Ser Lys Asn Gln Ser Trp Thr Arg
                                 90
Leu Ala Phe Ala Gly Leu Lys Phe Ala Asp Tyr Gly Ser Phe Asp Tyr
                            105
Gly Arg Asn Tyr Gly Val Met Tyr Asp Ile Glu Gly Trp Thr Asp Met
               120
                                            125
Leu Pro Glu Phe Gly Gly Asp Ser Tyr Thr Asn Ala Asp Asn Phe Met
                      135
Thr Gly Arg Ala Asn Gly Val Ala Thr Tyr Arg Asn Thr Asp Phe Phe
                  150
                                     155
Gly Leu Val Asn Gly Leu Asn Phe Ala Val Gln Tyr Gln Gly Asn Asn
               165
                                170
Glu Gly Ala Ser Asn Gly Gln Glu Gly Thr Asn Asn Gly Arg Asp Val
                             185
Arg His Glu Asn Gly Asp Gly Trp Gly Leu Ser Thr Thr Tyr Asp Leu
                         200
Gly Met Gly Phe Ser Ala Gly Ala Ala Tyr Thr Ser Ser Asp Arg Thr
                      215
                                         220
Asn Asp Gln Val Asn His Thr Ala Ala Gly Gly Asp Lys Ala Asp Ala
              230
                                     235
Trp Thr Ala Gly Leu Lys Tyr Asp Ala Asn Asn Ile Tyr Leu Ala Thr
               245
                                 250
Met Tyr Ser Glu Thr Arg Asn Met Thr Pro Phe Gly Asp Ser Asp Tyr
                              265
Ala Val Ala Asn Lys Thr Gln Asn Phe Glu Val Thr Ala Gln Tyr Gln
            280
Phe Asp Phe Gly Leu Arg Pro Ala Val Ser Phe Leu Met Ser Lys Gly
  290 295
Arg Asp Leu His Ala Ala Gly Gly Ala Asp Asn Pro Ala Gly Val Asp
                                    315
                   310
Asp Lys Asp Leu Val Lys Tyr Ala Asp Ile Gly Ala Thr Tyr Tyr Phe
           325
                                 330 335
Asn Lys Asn Met Ser Thr Tyr Val Asp Tyr Lys Ile Asn Leu Leu Asp
                              345
Glu Asp Asp Ser Phe Tyr Ala Ala Asn Gly Ile Ser Thr Asp Asp Ile
      355 ·
Val Ala Leu Gly Leu Val Tyr Gln Phe
                       375
<210> 451
<211> 1122
<212> PRT
<213> Escherichia coli
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                                  10
Met Glu Phe Ile Val Glu Arg Glu Arg Leu Asp Asp Pro Phe Glu Pro
                              25
Glu Met Ile Leu Val Gln Ser Thr Gly Met Ala Gln Trp Leu Gln Met
                          40
Thr Leu Ser Gln Lys Phe Gly Ile Ala Ala Asn Ile Asp Phe Pro Leu
```

Pro 65	Ala	Ser	Phe	Ile	Trp 70	Asp	Met	Phe	Val	Arg 75	Val	Leu	Pro	Glu	Ile 80
Pro	Lys	Glu	Ser	Ala 85	Phe	Asn	Lys	Gln	Ser 90	Met	Ser	Trp	Lys	Leu 95	Met
			100					105					110	Leu	
His	Tyr	Leu 115	Thr	Asp	Asp	Ser	Asp 120	Lys	Arg	Lys	Leu	Phe 125	Gln	Leu	Ser
	130					135					140			Pro	
145					150					155					160
			•	165					170					Tyr 175	
			180					185					190	Gln	
		195					200					205		Leu	
	210				_	215					220			Tyr	
225					230	3.				235	:				240
				245				·	250				•	Ala 255	
		_	260					265					270	Asp	
		275			_	_	280					285		Phe	
	290	_				295					300			Trp	
305					310					315				Ser	320
			_	325					330					Leu 335	
			340	_				345					350	Ala	
		355					360					365		Leu	
	370	_				375					380			Gln	
385					390		-			395				Glu	400
Pro	Thr	Leu	Thr	Pro 405	Arg	Asp	Ile	Ile	Val 410	Met	Val	Ala	Asp	Ile 415	Asp
Ser	Tyr	Ser	Pro 420	Phe	Ile	Gln	Ala	Val 425	Phe	Gly	Ser	Ala	Pro 430	Ala	Asp
Arg	Tyr	Leu 435	Pro	Tyr	Ala	Ile	Ser 440	Asp	Arg	Arg	Ala	Arg 445	Gln	Ser	His
	450					455					460			Ser	
Phe 465	Val	Ser	Glu	Asp	Val 470	Leu	Ala	Leu	Leu	Asp 475	Val	Pro	Val	Leu	Ala 480
Ala	Arg	Phe	Asp	Ile 485	Thr	Glu	Glu	Gly	Leu 490	Arg	Tyr	Leu	Arg	Gln 495	Trp
Val	Asn	Glu	Ser 500	Gly	Ile	Arg	Trp	Gly 505	Ile	Asp	Asp	Asp	Asn 510	Val	Arg
Glu	Leu	Glu 515		Pro	Ala	Thr	Gly 520	Gln	His	Thr	Trp	Arg 525	Phe	Gly	Leu
Thr	Arg 530	Met	Leu	Leu	Gly	Tyr 535	Ala	Met	Glu	Ser	Ala 540	Gln	Gly	Glu	Trp

Gln 545	Ser	Val	Leu	Pro	Tyr 550	Asp	Glu	Ser	Ser	Gly 555	Leu	Ile	Ala	Glu	Leu 560
	Gly	His	Leu	Ala 565		Leu	Leu	Met	Gln 570		Asn	Ile	Trp	Arg 575	
Gly	Leu	Ala	Gln 580		Arg	Pro	Leu	Glu 585		Trp	Leu	Pro	Val 590		Arg
Asp	Met	Leu 595	Asn	Ala	Phe	Phe	Leu 600		Asp	Ala	Glu	Thr 605		Ala	Ala
Met	Thr 610	Leu	Ile	Glu	Gln	Gln 615	Trp	Gln	Ala	Ile	Ile 620		Glu	Gly	Leu
Gly 625	Ala	Gln	Tyr	Gly	Asp 630	Ala	Val	Pro	Leu	Ser 635	Leu	Leu	Arg	Asp	Glu 640
Leu	Ala	Gln	Arg	Leu 645	Asp	Gln	Glu	Arg	11e 650	Ser	Gln	Arg	Phe	Leu 655	Ala
_			Asn 660		_			665			_		670		
		675	Cys				680					685		_	
	690		Leu			695					700		_	_	
705			Arg		710			-		715					720
			Gln	725					730			_		735	
	_		Ser 740					745					750		
		755	Gly				760				_	765			
	770		Ser			775					780				
785			Pro		790					795				_	800
			Arg	805					810				_	815	
His	Ser	Glu	Phe 820	Val	Gln	Pro	Leu	Pro 825	Phe	Thr	Leu	Pro	Glu 830	Thr	Val
		835	Thr				840					845	_		
	850		Arg			855					860				
Pro 865	Asp	Thr	Glu	Pro	Phe 870	Ile	Leu	Glu	Gly	Leu 875	Ser	Arg	Tyr	Gln	Ile 880
Asn	Gln	Gln	Leu	Leu 885						Gln	_	_	Ala	Glu 895	Arg
Leu	Phe	Arg	Arg 900	Phe	Arg	Ala	Ala	Gly 905	Asp	Leu	Pro	Tyr	Gly 910	Ala	Phe
_		915	Phe	_			920					925			
Asp	Arg 930	Val	Ile	Ala	Cys	Arg 935	Gln	Pro	Gly	Gln	Ser 940	Met	Glu	Ile	Asp
Leu 945	Ala	Cys	Asn	Gly	Val 950	Gln	Ile	Thr	Gly	Trp 955	Leu	Pro	Gln	Val	Gln 960
Pro	Asp	Gly	Leu	Leu 965	Arg	Trp	Arg	Pro	Ser 970	Leu	Leu	Ser	Val	Ala 975	Gln
Gly	Met	Gln	Leu 980	Trp	Leu	Glu	His	Leu 985	Val	Tyr	Cys	Ala	Ser 990	Gly	Gly
Asn	Gly	Glu 995	Ser	Arg	Leu	Phe	Leu 1000	_	Lys	Asp	Gly	Glu 1009		Arg	Phe
Pro	Pro 1010		Ala	Ala	Glu	Gln 101		Leu	His	Tyr	Leu 1020		Gln	Leu	Ile

Glu Gly Tyr Arg Glu Gly Met Ser Ala Pro Leu Leu Val Leu Pro Glu 1035 1030 Ser Gly Gly Ala Trp Leu Lys Thr Cys Tyr Asp Ala Gln Asn Asp Ala 1050 1045 Met Leu Asp Asp Asp Ser Thr Leu Gln Lys Ala Arg Thr Lys Phe Leu 1060 1065 1070 Gln Ala Tyr Glu Gly Asn Met Met Val Arg Gly Glu Gly Asp Asp Ile 1080 1085 1075 Trp Tyr Gln Arg Leu Trp Arg Gln Leu Thr Pro Glu Thr Met Glu Ala 1095 1100 Ile Val Glu Gln Ser Gln Arg Phe Leu Leu Pro Leu Phe Arg Phe Asn 1110 Gln Ser <210> 452 <211> 107

<211> 107 <212> PRT <213> Escherichia coli

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<210> 453 <211> 121 <212> PRT <213> Escherichia coli

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<210> 454

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<213> Escherichia coli
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Met Ala Ile Ser Ser Val Leu Leu Gly Ala Ala Arg Phe Leu Pro
                             25
Ala Leu Gln Arg Glu Ser Leu Thr Ser Thr Arg Lys Leu Ala Leu Glu
                      40
Asp Glu Ile Trp Leu Arg Val Phe Thr Val Ala Lys His Leu Gln Arg
                      55
                                        60
Ala Gly Tyr Cys His Gly Ile Cys Thr Gly Glu Gly Leu Glu Ile Val
Gly Gln Gly Asp Cys Val Ile Val Gln Trp Asp Ala Asn Ser Asn Gly
              85
                                 90
Ile Trp Asp Arg Glu Pro Val Lys Glu Ser Asp Gln Ile Gly Phe Arg
           100
                             105
                                                110
Leu Lys Glu His Val Leu Glu Thr Leu Arg Gly Ala Thr Ser Cys Glu
                          120
      115
Gly Lys Gly Trp Asp Lys Val Thr Asn Pro Asp Ala Ile Ile Ile Asp
                    135
                                        140
Thr Phe Gln Val Val Arg Gln Asp Val Ser Gly Phe Ser Pro Val Leu
        150 155 160
Thr Val Asn Met Arg Ala Ala Ser Lys Ser Glu Pro Gln Thr Val Val
             165
                                170
Asn Ala Ser Tyr Ser Val Thr Gly Phe Asn Leu
           180
                              185
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<213> Escherichia coli
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Leu Ile Leu Val Met Leu Ser Ala Ser Gly Leu Tyr Gly Trp Gln Tyr
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                              25
Trp Gln Gln Ser Gln Arg Leu Trp Gln Thr Ala Ser Gln Ala Arg Asp
                          40
Tyr Leu Leu Tyr Leu Arg Glu Asp Ala Asn Trp His Asn Arg Asp His
                     55
                                         60
Ser Ile Ser Val Ile Arg Glu Gly Thr Leu Trp Cys Leu Val Ser Ser
                  70
                                   75
Ala Ala Gly Ala Asn Thr Cys His Gly Ser Ser Pro Leu Val Phe Val
                                  90
Pro Arg Trp Pro Glu Val Glu Met Ser Asp Leu Thr Pro Ser Leu Ala
                              105
Phe Phe Gly Leu Arg Asn Thr Ala Trp Ala Gly His Ile Arg Phe Lys
                         120
                                            125
Asn Ser Thr Gly Glu Trp Trp Leu Val Val Ser Pro Trp Gly Arg Leu
                     135
                                        140
Arg Leu Cys Gln Gln Gly Glu Thr Glu Gly Cys Leu
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<210> 456
<211> 711
<212> PRT
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-408-

<213> Escherichia coli

<400> 456 Met Ser Thr Ile Val Ile Phe Leu Ala Ala Leu Leu Ala Cys Ser Leu Leu Ala Gly Trp Leu Ile Lys Val Arg Ser Arg Arg Gln Leu Pro 25 Trp Thr Asn Ala Phe Ala Asp Ala Gln Thr Arg Lys Leu Thr Pro Glu 40 45 Glu Arg Ser Ala Val Glu Asn Tyr Leu Glu Ser Leu Thr Gln Val Leu 55 Gln Val Pro Gly Pro Thr Gly Ala Ser Ala Ala Pro Ile Ser Leu Ala 70 75 Leu Asn Ala Glu Ser Asn Asn Val Met Met Leu Thr His Ala Ile Thr 90 Arg Tyr Gly Ile Ser Thr Asp Asp Pro Asn Lys Trp Arg Tyr Tyr Leu 105 110 Asp Ser Val Glu Val His Leu Pro Pro Phe Trp Glu Gln Tyr Ile Asn 120 Asp Glu Asn Thr Val Glu Leu Ile His Thr Asp Ser Leu Pro Leu Val 135 140 Ile Ser Leu Asn Gly His Thr Leu Gln Glu Tyr Met Gln Glu Thr Arg 150 155 Ser Tyr Ala Leu Gln Pro Val Pro Ser Thr Gln Ala Ser Ile Arg Gly 165 170 175 Glu Glu Ser Glu Gln Ile Glu Leu Leu Asn Ile Arg Lys Glu Thr His 185 190 Glu Glu Tyr Ala Leu Ser Arg Pro Arg Gly Leu Arg Glu Ala Leu Leu 195 200 Ile Val Ala Ser Phe Leu Met Phe Phe Phe Cys Leu Ile Thr Pro Asp 215 220 Val Phe Val Pro Trp Leu Ala Gly Gly Ala Leu Leu Leu Gly Ala 230 Gly Leu Trp Gly Leu Phe Ala Pro Pro Ala Lys Ser Ser Leu Arg Glu 245 250 Ile His Cys Leu Arg Gly Thr Pro Arg Arg Trp Gly Leu Phe Gly Glu 265 Asn Asp Gln Glu Gln Ile Asn Asn Ile Ser Leu Gly Ile Ile Asp Leu 280 Val Tyr Pro Ala His Trp Gln Pro Tyr Ile Ala Gln Asp Leu Gly Gln 295 Gln Thr Asp Ile Asp Ile Tyr Leu Asp Arg His Val Val Arg Gln Gly 310 315 Arg Tyr Leu Ser Leu His Asp Glu Val Lys Asn Phe Pro Leu Gln His 330 325 Trp Leu Arg Ser Thr Ile Ile Ala Ala Gly Ser Leu Leu Val Leu Phe 340 345 Met Leu Leu Phe Trp Ile Pro Leu Asp Met Pro Leu Lys Phe Thr Leu 360 365 Ser Trp Met Lys Gly Ala Gln Thr Ile Glu Ala Thr Ser Val Lys Gln 375 380 Leu Ala Asp Ala Gly Val Arg Val Gly Asp Thr Leu Arg Ile Ser Gly 390 395 Thr Gly Met Cys Asn Ile Arg Thr Ser Gly Thr Trp Ser Ala Lys Thr 405 410 415 Asn Ser Pro Phe Leu Pro Phe Asp Cys Ser Gln Ile Ile Trp Asn Asp 425 420 Ala Arg Ser Leu Pro Leu Pro Glu Ser Glu Leu Val Asn Lys Ala Thr 440 Ala Leu Thr Glu Ala Val Asn Arg Gln Leu His Pro Lys Pro Glu Asp

460

455

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Glu Ser Arg Val Ser Ala Ser Leu Arg Ser Ala Ile Gln Lys Ser Gly
                  470
                                      475
Met Val Leu Leu Asp Asp Phe Gly Asp Ile Val Leu Lys Thr Ala Asp
                                  490
              485
Leu Cys Ser Ala Lys Asp Asp Cys Val Arg Leu Lys Asn Ala Leu Val
                              505
Asn Leu Gly Asn Ser Lys Asp Trp Asp Ala Leu Val Lys Arg Ala Asn
                          520
Ala Gly Lys Leu Asp Gly Val Asn Val Leu Leu Arg Pro Val Ser Ala
              535
                                540
Glu Ser Leu Asp Asn Leu Val Ala Thr Ser Thr Ala Pro Phe Ile Thr
         550
                           555
His Glu Thr Ala Arg Ala Ala Gln Ser Leu Asn Ser Pro Ala Pro Gly
              565
                                  570
Gly Phe Leu Ile Val Ser Asp Glu Gly Ser Asp Phe Val Asp Gln Pro
                               585
Trp Pro Ser Ala Ser Leu Tyr Asp Tyr Pro Pro Gln Glu Gln Trp Asn
                          600
Ala Phe Gln Lys Leu Ala Gln Met Leu Met His Thr Pro Phe Asn Ala
                      615
                                          620
Glu Gly Ile Val Thr Lys Ile Phe Thr Asp Ala Asn Gly Thr Gln His
                  630
                                     635
Ile Gly Leu His Pro Ile Pro Asp Arg Ser Gly Leu Trp Arg Tyr Leu
              645
                                  650
Ser Thr Thr Leu Leu Leu Leu Thr Met Leu Gly Ser Ala Ile Tyr Asn
                             665
Gly Val Gln Ala Trp Arg Arg Tyr Gln Arg His Arg Thr Arg Met Met
                          680
Glu Ile Gln Ala Tyr Tyr Glu Ser Cys Leu Asn Pro Gln Leu Ile Thr
                    695
Pro Ser Glu Ser Leu Ile Glu
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<211> 237
<212> PRT
<213> Escherichia coli
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Met Leu Pro Cys Arg Ala Asn Cys Phe Thr Leu Glu Ile Ser Leu Met
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His Ile Asn Ile Ala Trp Gln Asp Val Asp Thr Val Leu Leu Asp Met
Asp Gly Thr Leu Leu Asp Leu Ala Phe Asp Asn Tyr Phe Trp Gln Lys
                           40
Leu Val Pro Glu Thr Trp Gly Ala Lys Asn Gly Val Thr Pro Gln Glu
                      55
Ala Met Glu Tyr Met Arg Gln Gln Tyr His Asp Val Gln His Thr Leu
Asn Trp Tyr Cys Leu Asp Tyr Trp Ser Glu Gln Leu Gly Leu Asp Ile
                                  90
Cys Ala Met Thr Thr Glu Met Gly Pro Arg Ala Val Leu Arg Glu Asp
          100
                              105
Thr Ile Pro Phe Leu Glu Ala Leu Lys Ala Ser Gly Lys Gln Arg Ile
                          120
Leu Leu Thr Asn Ala His Pro His Asn Leu Ala Val Lys Leu Glu His
                       135
                                          140
Thr Gly Leu Asp Ala His Leu Asp Leu Leu Leu Ser Thr His Thr Phe
                   150
                                      155
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```
Gly Tyr Pro Lys Glu Asp Gln Arg Leu Trp His Ala Val Ala Glu Ala
              165 . 170
Thr Gly Leu Lys Ala Glu Arg Thr Leu Phe Ile Asp Asp Ser Glu Ala
                            185
          180
Ile Leu Asp Ala Ala Ala Gln Phe Gly Ile Arg Tyr Cys Leu Gly Val
                                  . 205
                          200
Thr Asn Pro Asp Ser Gly Ile Ala Glu Lys Gln Tyr Gln Arg His Pro
                       215
Ser Leu Asn Asp Tyr Arg Arg Leu Ile Pro Ser Leu Met
                   230
<210> 458
<211> 133
<212> PRT
<213> Escherichia coli
<400> 458
Met Lys Glu Lys Pro Ala Val Glu Val Arg Leu Asp Lys Trp Leu Trp
                                  10
Ala Ala Arg Phe Tyr Lys Thr Arg Ala Leu Ala Arg Glu Met Ile Glu
           20
                               25
Gly Gly Lys Val His Tyr Asn Gly Gln Arg Ser Lys Pro Ser Lys Ile
Val Glu Leu Asn Ala Thr Leu Thr Leu Arg Gln Gly Asn Asp Glu Arg
Thr Val Ile Val Lys Ala Ile Thr Glu Gln Arg Arg Pro Ala Ser Glu
                  70
Ala Ala Leu Leu Tyr Glu Glu Thr Ala Glu Ser Val Glu Lys Arg Glu
                                  90
Lys Met Ala Leu Ala Arg Lys Leu Asn Ala Leu Thr Met Pro His Pro
                              105
Asp Arg Arg Pro Asp Lys Lys Glu Arg Arg Asp Leu Leu Arg Phe Lys
                          120
His Gly Asp Ser Glu
  130
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<211> 294
<212> PRT
<213> Escherichia coli
<400> 459
Met Ile Met Pro Gln His Asp Gln Leu His Arg Tyr Leu Phe Glu Asn
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Phe Ala Val Arg Gly Glu Leu Val Thr Val Ser Glu Thr Leu Gln Gln
                               25
Ile Leu Glu Asn His Asp Tyr Pro Gln Pro Val Lys Asn Val Leu Ala
                           40
Glu Leu Leu Val Ala Thr Ser Leu Leu Thr Ala Thr Leu Lys Phe Asp
                       55
                                           60
Gly Asp Ile Thr Val Gln Leu Gln Gly Asp Gly Pro Met Asn Leu Ala
                                       75
                  70
Val Ile Asn Gly Asn Asn Asn Gln Gln Met Arg Gly Val Ala Arg Val
                                   90
               85
Gln Gly Glu Ile Pro Glu Asn Ala Asp Leu Lys Thr Leu Val Gly Asn
                               105
Gly Tyr Val Val Ile Thr Ile Thr Pro Ser Glu Gly Glu Arg Tyr Gln
                           120
                                               125
Gly Val Val Gly Leu Glu Gly Asp Thr Leu Ala Ala Cys Leu Glu Asp
                       135
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Tyr Phe Met Arg Ser Glu Gln Leu Pro Thr Arg Leu Phe Ile Arg Thr
                                    155
                  150
Gly Asp Val Asp Gly Lys Pro Ala Ala Gly Gly Met Leu Leu Gln Val
                                   170
               165
Met Pro Ala Gln Asn Ala Gln Gln Asp Asp Phe Asp His Leu Ala Thr
                               185
           180
Leu Thr Glu Thr Ile Lys Thr Glu Glu Leu Leu Thr Leu Pro Ala Asn
                           200
Glu Val Leu Trp Arg Leu Tyr His Glu Glu Glu Val Thr Val Tyr Asp
                   215
                                          220
Pro Gln Asp Val Glu Phe Lys Cys Thr Cys Ser Arg Glu Arg Cys Ala
                  230
                                      235
Asp Ala Leu Lys Thr Leu Pro Asp Glu Glu Val Asp Ser Ile Leu Ala
                                  250
Glu Asp Gly Glu Ile Asp Met His Cys Asp Tyr Cys Gly Asn His Tyr
                           265
Leu Phe Asn Ala Met Asp Ile Ala Glu Ile Arg Asn Asn Ala Ser Pro
                           280
Ala Asp Pro Gln Val His
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<211> 120
<212> PRT
<213> Escherichia coli
<400> 460
Met Leu Lys Leu Phe Ala Lys Tyr Thr Ser Ile Gly Val Leu Asn Thr
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Leu Ile His Trp Val Val Phe Gly Val Cys Ile Tyr Val Ala His Thr
          20
Asn Gln Ala Leu Ala Asn Phe Ala Gly Phe Val Val Ala Val Ser Phe
Ser Phe Phe Ala Asn Ala Lys Phe Thr Phe Lys Ala Ser Thr Thr Thr
Met Arg Tyr Met Leu Tyr Val Gly Phe Met Gly Thr Leu Ser Ala Thr
                70
Val Gly Trp Ala Ala Asp Arg Cys Ala Leu Pro Pro Met Ile Thr Leu
              85
Val Thr Phe Ser Ala Ile Ser Leu Val Cys Gly Phe Val Tyr Ser Lys
                              105
Phe Ile Val Phe Arg Asp Ala Lys
       115
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<211> 306
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Met Lys Ile Ser Leu Val Val Pro Val Phe Asn Glu Glu Glu Ala Ile
1
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-414-

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English

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- (81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS. JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR. IE, IT. LU. MC. NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GENES ESSENTIAL FOR MICROBIAL PROLIFERATION

(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms as well as to screen for antimicrobial agents.

INTERNATIONAL SEARCH REPORT

Intern Tal Application No PCT/US 00/30950

			0/30330		
A. CLASS IPC 7	FICATION OF SUBJECT MATTER C12N15/31 C12N15/11 C12N1	5/10 C07K14/245			
According t	to International Patent Classification (IPC) or to both national class	sification and IPC			
	SEARCHED		· · · · · · · · · · · · · · · · · · ·		
Minimum di IPC 7	ocumentation searched (classification system followed by classifi C12N C07K	cation symbols)			
Documenta	tion searched other than minimum documentation to the extent th	at such documents are included in the fields so	earched		
	lata base consulted during the international search (name of data)		
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.		
Х	DATABASE EM_PRO [Online] EMBL; 29 January 1997 (1997-01- BLATTNER ET AL.: "Escherichia of MG1655 section 101 of 400 of the genome"	coli K12	5,10,13, 14, 18-21, 124		
.,	retrieved from EBI, accession r Database accession no. AE000211 XP002181472 the whole document		1 121		
Y X	-& DATABASE SWALL [Online] 15 July 1998 (1998-07-15) BLATTNER ET AL.: "Hypothetical YCFS precursor" retrieved from EBI, accession n YCFS ECOLI	1-131 5,10,13, 14, 18-21, 124			
	Database accession no. P75954 XP002181473 the whole document	-/			
X Funi	ner documents are listed in the continuation of box C.	Y Patent family members are listed in	n annex.		
<u> </u>	tegories of cited documents :	"T" later document published after the inter			
"A" document defining the general state of the art which is not considered to be of particular relevance or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or after the international or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention or priority date and not in conflict with the application but cited to understand the principle or the principle or the principle or the principle or the art which is not considered to understand the principle or the principle or the art which is not considered to understand the principle or the art which is not considered to understand the principle or the art which is not considered to understand the principle or the art which is not considered to understand the principle or the art which is not considered to understand the principle or the art which is not considered to understand the principle					
which citation	ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another nor other special reason (as specified) ent referring to an oral disclosure, use, exhibition or	cannot be considered novel or cannot limitative an inventive step when the doc "Y" document of particular relevance; the ci- cannot be considered to involve an invi- document is combined with one or mor- ments, such combination being obviou-	De considered to ument is taken alone aimed invention entire step when the e other such docu-		
later th	ent published prior to the international filling date but nan the priority date claimed	in the art. "&" document member of the same patent for			
	actual completion of the international search 5 November 2001	Oate of mailing of the international sear	ch report		
Name and r	nailing address of the ISA European Patent Office, P.B. 5818 Patentilaan 2 NL - 2280 HV Rijswijk Tel (#31-77) 340-940, Tx 31 651 epo pl	Authorized officer			
	Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Ceder, O			

INTERNATIONAL SEARCH REPORT

Interm nat Application No PCT/US 00/30950

tegory *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	-& DATABASE EM_PRO [Online] EMBL; 29 January 1997 (1997-01-29) BLATTNER ET AL.: "Escherichia coli K12 MG1655 section 305 of 400 of the complete genome" retrieved from EBI, accession no. ECAE415	5,10,13, 14, 18-21, 124
	Database accession no. AE000415 XP002181474 the whole document	
Ķ	-& DATABASE SWALL [Online] 1 November 1995 (1995-11-01) BLATTNER ET AL.: "Hypothetical 79.5 kDa protein in MRCA-PCKA intergenic region (0711)" retrieved from EBI, accession no.	5,10,13, 14, 18-21, 124
1	YRFF ECOLI Database accession no. P45800 XP002181475 the whole document -& BLATTNER ET AL.: "The complete genome	1,9
	sequence of Escherichia coli K-12" SCIENCE, vol. 277, 5 September 1997 (1997-09-05), pages 1453-1462, FIFURES, XP002923023 the whole document	
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INT" PNATIONAL SEARCH REPORT

Intern all Application No
PCT/US 00/30950

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C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
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E	WO 01 48209 A (OHLSEN KARI L ;FORSYTH R ALLYN (US); ELITRA PHARMACEUTICALS INC (U) 5 July 2001 (2001-07-05) page 3 -page 14 seq id nos 274, 467	1-131
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INTERNATIONAL SEARCH REPORT

In ational application No. PCT/US 00/30950

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: See FURTHER INFORMATION sheet PCT/ISA/210
2. X Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet As a result of the prior review under R. 40.2(e) PCT, part of the additional fees are to be refunded.
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. X As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-131 (Seq Id Nos 1, 116, 128, 285, 299, 456) 4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest X The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 129-131 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Present claims 36, 44, 57, 95, 98, 109 and 117 relate to a compound defined by reference to a desirable characteristic or property, namely being identifiable by using the method of claims 28, 38, 45, 84, 96, 99, or 110, respectively. Present claims 125 and 126 relate to a compound defined by reference to a desirable characteristic or property, namely interacting with a gene or gene product or a polypeptide whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOS 1-127.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the sequences of claims 1, 9 and 19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 12-14, 45-124, 129-130 all partially

Invention 1:

A purified or isolated nucleic acid sequence, consisting of Seq Id No 1, a vector comprising said sequence, a host cell containing said vector, and their uses.

2. Claims: 1-8, 12-14, 45-124, 129-130 all partially

Inventions 2 to 127:

Idem as invention 1, but for Seq Id Nos 2-127, respectively.

3. Claims: 9-11, 15-44, 125-128 all partially

Invention 128:

A purified or isolated nucleic acid sequence consisting of Seq Id No 128, a vector comprising said sequence, a host cell containing said vector, a polypeptide encoded by said nucleic acid sequence and having Seq Id No 299, and an antibody binding said polypeptide, and their uses.

4. Claims: 9-11, 15-44, 125-128 all partially

Inventions 129 to 298:

Idem as invention 128, but for nucleic acid Seq Id Nos 129-298 and corresponding polypeptide Seq Id Nos 300-469, respectively.

INTERNATIONAL SEARCH REPORT

information on patent family members

Intern nal Application No PCT/US 00/30950

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